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Special Issue

University of Michigan Medical School

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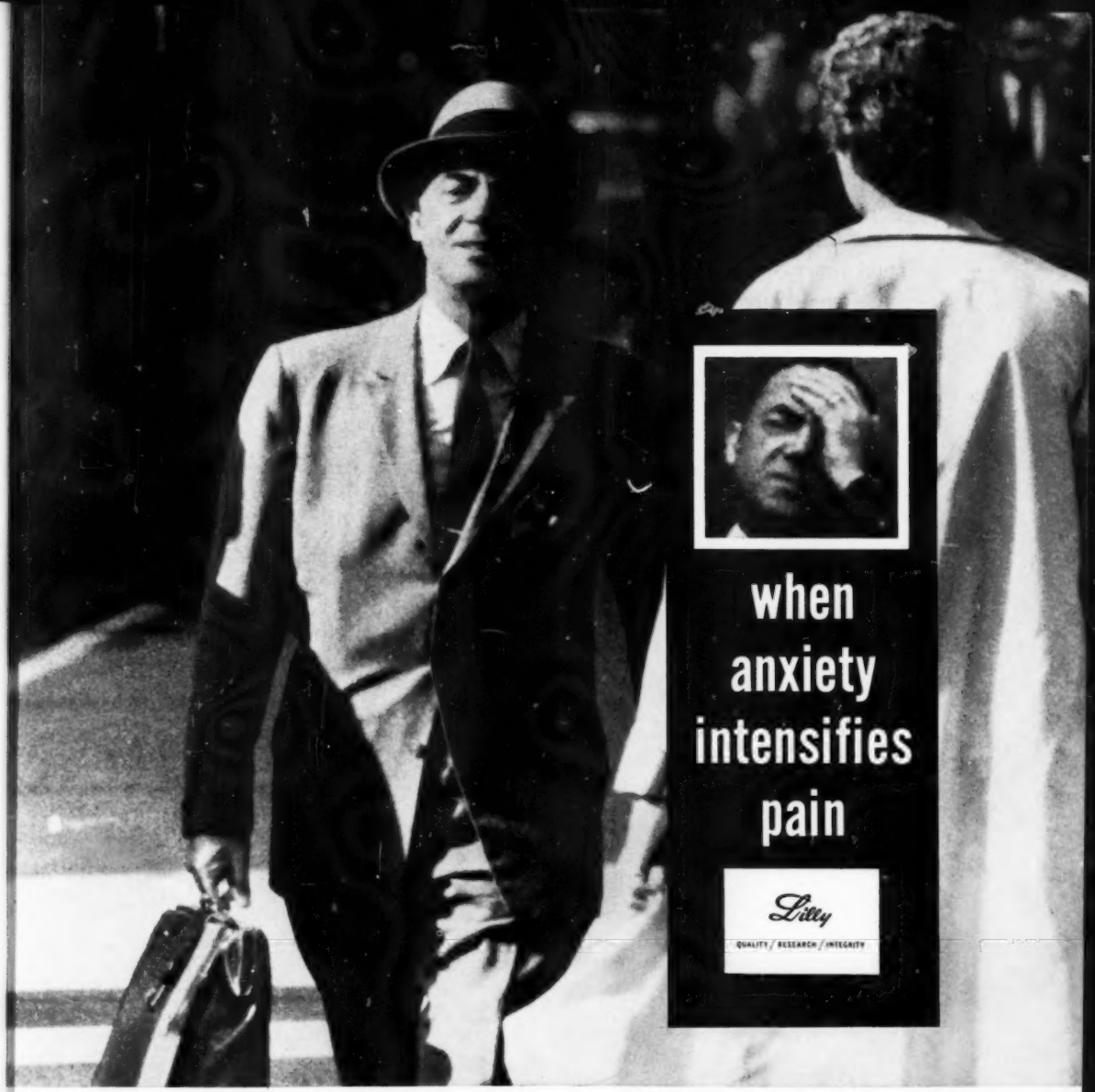

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• UPPER RESPIRATORY TRACT INFECTIONS

Q. In treating routine office cases of infections due to penicillin-sensitive organisms, such as tonsillitis or otitis media, what are the relative merits of the following forms of penicillin: orally administered penicillin G, penicillin V and penicillin VK and parenterally administered procaine penicillin G in aqueous suspension and benzathine penicillin G? What dosage of each would be equally effective? Is orally administered penicillin VK sufficiently superior to orally administered penicillin GK to counterbalance the great difference in the prescription cost to the patient? What form of penicillin therapy would be indicated in tonsillitis due to a hemolytic *Streptococcus*, assuming there are no complications? Would this therapy be the same for an adult as it would be for a six year old child?

M.D.—Pennsylvania

A. The preferred treatment for streptococcic pharyngitis and tonsillitis is benzathine penicillin G (BICILLIN®, PERMAPEN®) given in a single intramuscular injection of 600,000 units for children and 900,000 units for adults. When given in sufficient amounts over a 10 day period, procaine penicillin G also has been effective. Both the buffered salt of penicillin G and phenoxymethyl penicillin given orally in a dosage of 250,000 to 500,000 units four times daily for 10 days have brought about satisfactory results. The main advantage of the intramuscular route of administration is the assurance that the patient will receive the intended therapy. It has been shown that patients often do not take the orally administered medicine as prescribed.

Additional details regarding the treatment of infections of the upper respiratory tract can be found in the report of F. W. Denny, Jr. and J. H. Dingle on the current status of therapy in upper respiratory infections. (J.A.M.A. 166:1595-1602 [March 29] 1958.)

• "BIRD FOOD"

Q. Several of my patients are eating a bird food mixture with the idea that its high vitamin content helps to lessen afternoon fatigue. They eat about 1 oz. of the following for lunch: equal parts sunflower seeds, squash seeds (papita), seedless raisins and gristmill dry cereal. This preparation is sometimes taken with milk, tea, coffee or water. What is the approximate vitamin content of this mixture?

M.D.—New York

A. The consumption of this mixture is an example of dietary fads. While this one does not seem to be harmful as such, it may detract from the consumption of an otherwise well-balanced diet providing the necessary nutrients. Seedless raisins are a source of carbohydrate with some calcium, phosphorus, iron and carotene; however, ¼ oz. would provide only 0.25 mg. iron, 3.75 I.U. vitamin A, 0.01 mg. thiamine, 0.006 mg. riboflavin, 0.04 mg. niacin, and only traces of vitamin C. While this is a pleasant-tasting food, it does not have any unusual nutritional qualities.

Squash seeds are a source of protein and fat; they also contain calcium, phosphorus, iron and very small traces of B vitamins. One-fourth table-

(Continued on page A-20)

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Data on sunflower seeds are not readily available, but in this relatively small amount they provide a few grams of protein and carbohydrate and some limited amounts of vitamins and minerals. While by no means noxious, they do not contribute anything to a well-balanced diet.

• EXCESSIVE SLEEPINESS

Q. A 44 year old married white woman has lethargy and somnolence to the degree that in making short trips she must stop driving and sleep. She has no other symptoms. A blood count, urinalysis, blood pressure reading, and determinations of the basal metabolic rate and the protein-bound iodine gave essentially normal findings. The patient works as a bookkeeper 10 or 12 hours a day and must use WYAMINE® and similar drugs to keep awake.

What is the probable diagnosis in this case and what further medical investigation should be carried out?

M.D.—Indiana

A. The complaint of recurrent and excessive sleepiness raises the question of the possible presence of narcolepsy. Originally thought to be a rare illness, narcolepsy has been recognized with increasing frequency in recent years. In the majority of patients, this excessive sleepiness is apparent either in adolescence or in young adulthood. Certain other symptoms occur rather consistently, including (1) cataplexy (found in two-thirds of narcoleptic patients), which consists of attacks of muscular weakness induced by emotions such as laughter, surprise or anger; (2) sleep paralysis (noted in about one-fourth of the patients), that is, brief episodes of inability to move when either awaking or falling asleep; (3) hypnagogic hallucinations (occurring in about one-third of the patients), which are vivid, dreamlike experiences appearing in the drifting phase between wakefulness and sleep. In only a minority of narcoleptic patients are all four symptoms present. About a fourth of the patients experience only excessive sleepiness. In this case, the patient should be questioned concerning these symptoms.

The diagnosis of narcolepsy is based on a carefully taken history. In this patient, the possibility of hypothyroidism already has been excluded by the determination of normal values for the basal metabolic rate and the protein-bound iodine.

Treatment consists of administering analeptic drugs, the most effective of which is methylphenidate (RITALIN® hydrochloride). The average patient requires 60 to 80 mg. daily in divided doses of 20 mg. each (Yoss, R. E. and Daly, D.: Treatment of narcolepsy with Ritalin. Neurology 9:171-173 [March] 1959). For maximal effect, Ritalin hydrochloride should be taken 30 minutes before meals, with the last dose not later than 6 P.M. to avoid insomnia.

• VOMITING IN INFANTS

Q. A six month old baby, very healthy and normal in size and weight, spits up excessively after each feeding. All available milks and some sedatives have been tried without benefit. The baby is not in any apparent discomfort. I would appreciate your advice.

M.D.—Ohio

A. The most common cause of spitting up in an infant is overdistention of the stomach by excessive feeding or excessive air swallowing or both. When spitting up or vomiting is on a pathologic basis, the baby will invariably be gaining weight poorly or even losing weight. Since the baby is "very healthy and normal in size and weight," this seems to be merely a problem of overdistention of the stomach. Management usually consists of smaller, more frequent feedings; if the baby tends to swallow air, attention should be given to the feeding, the nipple size, and technics in feeding. The mother should be reassured, and cautioned against overstimulating the baby immediately after feeding. Of course, the routine bubbling or burping helps expel excessive amounts of swallowed air. Some babies with a relaxed cardiac sphincter have a condition known as chalasia in which milk literally spills from the stomach into the esophagus and into the oropharynx when the baby is laid down after a feeding. This syndrome, however, appears in the early months of life and is usually well controlled by keeping the baby in a semisitting position for a period of time after each feeding. Generally, changing formulas and using sedatives and other medications do not help.

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1. Dunsmore, R.A., et al.: Am. J. M. Sc. *236*:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. *166*:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation *13*:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. *98*:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. *7*:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

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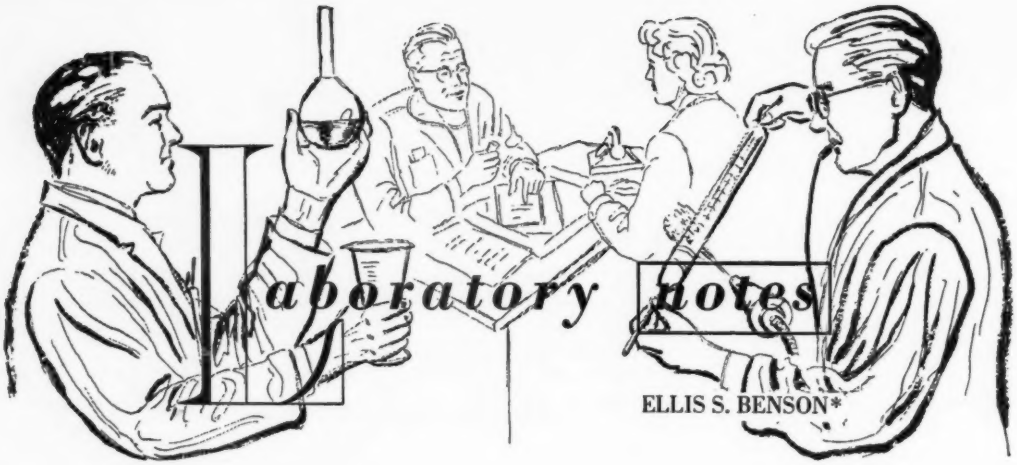

ELLIS S. BENSON*

Errors of Some Common Hematologic Measurements, Part 1

As an illustration of the absolute confidence frequently accorded the results of differential counts, Barnett[1] in 1933 quoted the following from an article on surgical lesions of the abdomen: "Probably the blood count is of the greatest value in determining the severity of the lesion in acute appendicitis. When the polymorphonuclear percentage is 70 or below, a suppurative or gangrenous process may be ruled out and operation delayed or postponed with safety. It is difficult to be sure of the severity of the process when the percentage of polymorphonuclears is between 70 and 80. I have seen beginning peritonitis with percentages below 80 but above this point one may feel sure that he is dealing with a dangerous lesion that should be treated immediately."

Barnett went on to state that such confidence is unwarranted, since differential counting is one of the most uncertain of the quantitative methods used in medicine. Are we much more sophisticated in this respect today? I think not, for although one finds in published articles less tendency toward sweeping generalizations based on hematologic measurements such as that quoted, the magic of numbers remains strong. Commonly, we are inclined to accept a reported result of the white blood cell count, red blood cell count, or differential count as a close approximation to the true numerical value. This tendency is of great importance in interpreting serial values of hematologic measurements, as illustrated in the following instance: An anemic patient was found to have a reticulocyte count of 1.5 per cent. She received treatment with one of the newer hematinic agents, and on the third day her reticulocyte count was 4 per cent. Is this a significant change?

During the two decades immediately following 1930, a literature arose on the subject of the inherent errors of quantitative hematologic measurements. Notable among the many important contributions was that of Magath, Berkson and Hurn.[2] It is not the purpose of this column to review in detail these contributions or to suggest that numerical reporting of white blood cell counts, red blood cell counts, differential counts, etc., is without value. I wish only to emphasize again the inherent errors of these measurements, the nature of these errors, and their importance to interpretation.

Magath, Berkson and Hurn[2] studied the inherent errors due to slight differences between

(Continued on page A-26)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

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Ayes, J.W. and Berlacher, F.J.: J.A.M.A. 169:109, (Jan. 10) 1959.

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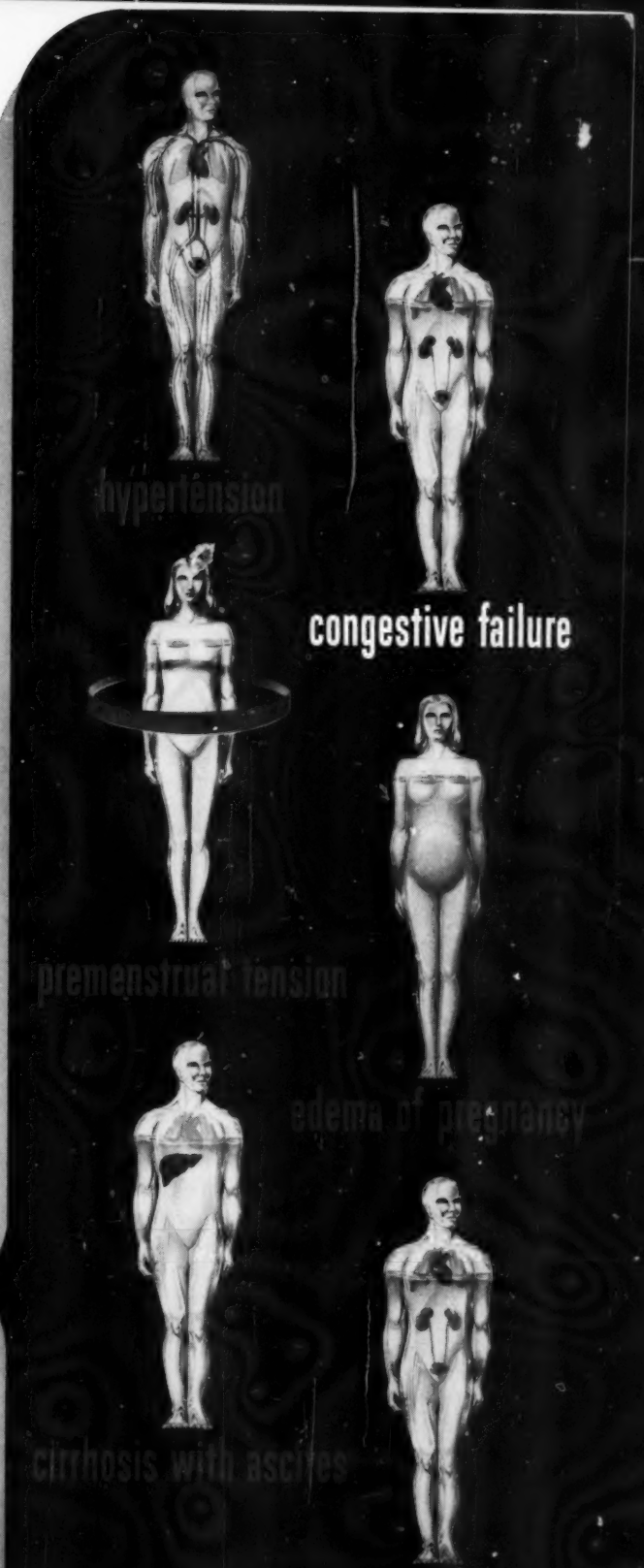

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pipets and counting chambers and the variations in distribution of red blood cells due to random settling in the counting chambers and random sampling. A technician of superior skill performed all technical maneuvers, and counting was done by photographing each field. In enlarged photographs, each cell was perforated with a stylus connected electrically with a recorder which registered the cell as it was pierced. Thus, technical errors were held to a minimum, and errors of counting by eye were eliminated. Pipets were calibrated within the limits of variation generally accepted, and the counting chambers were of the best quality. Under these conditions, which one must concede were ideal, the inherent error of the method was gauged. For a red blood cell concentration of five million per cubic millimeter, 95 per cent of measurements in which a single pipet and a single chamber are used should fall within the range 4,230,000 to 5,770,000 (15 per cent of five million in either direction from the mean). If all counts on blood containing five million cells per cubic millimeter were to be included, one would have to increase the range to from 3,845,000 to 6,155,000. Thus, purely by chance, a blood sample containing five million red cells per cubic millimeter may be counted as containing anywhere from 3,845,000 to 6,155,000 red blood cells per cubic millimeter.

This error is the so-called chance error due to small variations between pipets and counting chambers and to the fact that through random settling and random streaming the distribution of red blood cells throughout the counting chamber is nonuniform. In addition, counting the distribution in one small area gives us only an approximation of the over-all count in the chamber. This error also is augmented by the fact that the number of red blood cells in one sample of blood obtained from the patient may differ from the number in another sample obtained at the same time. This is the error of random sampling, which occurs whenever we deal with a universe composed of a very large number of individual units and our estimate of the frequency of the units is based on a study of an extremely small portion of that universe. This error can be decreased by increasing the size of the sample; however, practically speaking, it is never eliminated.

As an additional example of the scope of this problem, one might consider the differential count, a measurement which has come under critical scrutiny from time to time. Obviously, preparation of the blood smear for differential counting is of extreme importance. Different methods of preparing the smear, including various slide, cover-slip and slide-and-cover methods, have been proposed. All of these methods have their staunch advocates, but it is agreed that careful attention to the technic of smearing and staining the blood film is of paramount importance. Even when technic is good, however, variations in the individual distributions of the various types of leukocytes are apparent, with neutrophils tending to be distributed preferentially along the edges and in the tongues of the smear and lymphocytes in the central area.

A number of methods of counting have been advocated, colorful examples of which are the battlement method, an edge count, and the cross-sectional meander. None of these, of course, entirely eliminates errors due to nonuniform distribution. For example, suppose a patient's blood contains 50 per cent neutrophils. Successive counts based on examination of 100 cells at a time give per cent neutrophils of 42, 58, 49, 50, 42, 52, 47, 46, 39, 51, 58, 44, 57, etc. The most satisfactory way to express the degree of dispersion of these successive counts around the mean is to divide the sum of the squares of the differences between the individual observations and the mean value by the total number of observations and take the square root of the result. The value so obtained is known as the standard deviation (S.D.). Dividing the standard deviation by the mean value of all observations on material from one source and multiplying by 100 give us a value known as the coefficient of variation (CV). This is a very useful term, since it is expressed as a per cent of the mean. When the dispersion of the measurements describes a normal curve, as in figure 1, use of the coefficient of variation will al-

(Continued on page A-28)

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*Shane, S. J., Krzyski, T. Z., and Copp, S. E.: Canad. M.A.J. 77:600 (Sept. 15) 1957.

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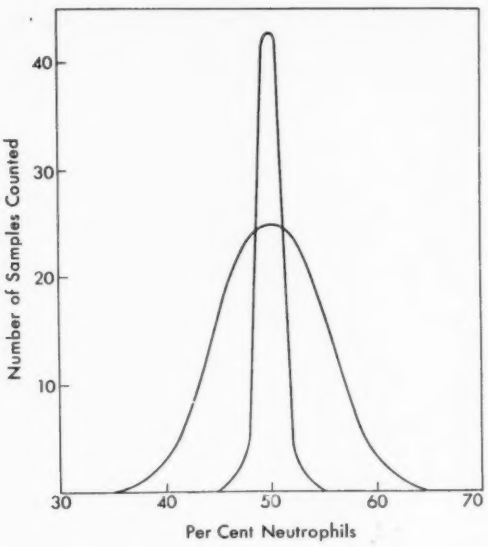

FIGURE 1. Variation in per cent neutrophils on successive counts made on a blood sample from a single source. Bell-shaped curves indicate the normal type of distribution of results around the mean. Note effect of size of sample inspected in each count on the distribution.

low us to establish what confidence can be placed in any single determination as to its precise meaning.

In the cited example of successive differential counts, the standard deviation is six cells per 100 and the coefficient of variation is 12 per cent ($CV = \frac{S.D.}{Mean} \times 100$). If the dispersion around the mean of these successive counts describes a normal curve, we know from probability theory that approximately two-thirds of all observations on samples from one source will fall within 1 S.D. of the mean; 95 per cent of all observations will fall within 2 S.D., and essentially all observations within 3 S.D. of the mean (figure 2).

Commonly, we wish to be confident that 95 per cent of measurements on samples from a given source will fall within a specified range, that is, from 2 S.D. below the mean to 2 S.D. above the mean. In the example cited, assuming that the first count in the series is the only measurement available and the coefficient of variation has been established as 12 per cent, one would make the following series of calculations: CV times the determined value equals $0.12 \times 42 = 5$; 5 is the S.D. Assuming that 42 is a mean value, 95 per cent of measurements would fall in the range 32 to 52. One thus predicts that the true value represented by this measurement lies somewhere within this range. A subsequent measurement which lies outside this range might be considered as representing a significant change. Note that classifying 100 leukocytes does not permit much accuracy in predicting the true mean and significant fluctuations from it, as this example illustrates. Some improvement would be obtained by enlarging the sample to 200 or 500 cells (figure 1).

The observations of Magath, Berkson and

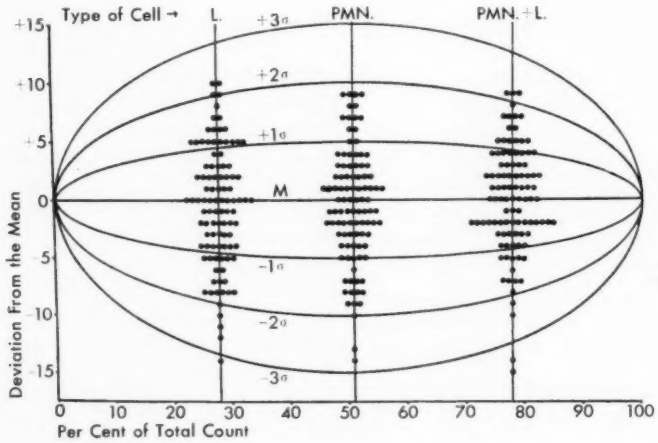

FIGURE 2. Chart showing the deviation of individual counts of neutrophils (PMN.) and lymphocytes (L.) from the mean (M) in relation to multiples of the standard deviation (σ [S.D.]). Note that 1 S.D. from the mean in either direction ($+1\sigma$ to -1σ) includes approximately two-thirds of the observations, while the area within $+2\sigma$ and -2σ includes about 90 per cent of observations.

(Reproduced by courtesy of Dr. C. W. Barnett.[3])

(Continued on page A-30)

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Hurn[2] represented a strategic attack on this problem; however, since technical errors were minimized and errors due to counting by eye eliminated, their data regarding coefficients of variation, etc., obviously cannot be translated directly to describe the magnitude of error in red cell counting in ordinary laboratory practice. Realizing this, Biggs and MacMillan[3] conducted a study in which they attempted to assess the errors of some common hematologic measurements in ordinary routine practice.

In next month's column I shall continue this discussion by reviewing the experiences of Biggs and MacMillan and others and by discussing some points of practical significance in applying these observations.

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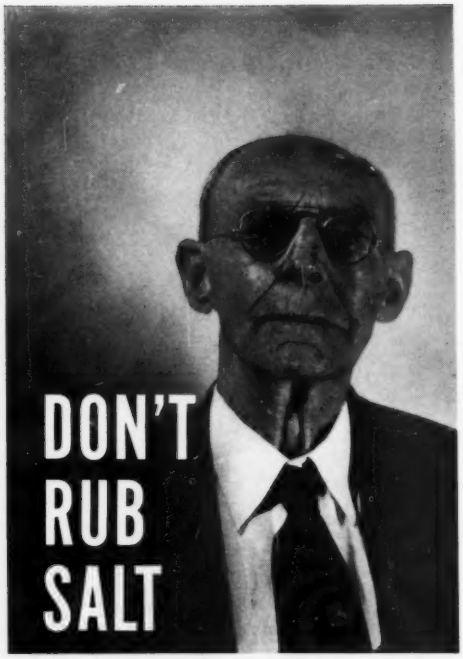

IN HIS CARDIAC WOUND

Modern saluretics may *seem* to have made unlimited salt intake possible for cardiac and hypertensive patients. Yet despite the improvements in diuretic therapy, sodium restriction is still important in the prophylaxis of edema. The wise physician does not add needlessly to the burden of his patient, nor test unnecessarily the power of the drugs he prescribes. It makes good sense to him to prescribe DIASAL—which looks, tastes and flavors food exactly like salt . . . but is sodium free.

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Central Association of Obstetricians and Gynecologists:

- An attempt was made to investigate that small group of patients who reveal no evidence of physiologic abnormality and yet have not achieved pregnancy. Antibodies have been detected in cervical and nasal secretions, tears, saliva and bile. This supports recent findings that the male is capable of elaborating antigens attached to the sperm.—Dr. S. J. Behrman, University of Michigan Medical School, Ann Arbor.
- Injectable iron-dextran gave a more rapid and consistent improvement in the treatment of anemia in the gravid patient than did an orally administered preparation containing ferrous sulfate and vitamin C. A total of 225 patients received sufficient treatment to be included in this study.—Dr. Fred B. Hapke, Columbus.
- A potent pressor polypeptide, hysterotonin, has been discovered in the amniotic fluid and decidua of toxemic patients. The substance appears to be the product of enzymatic activity localized in the decidua.—Dr. Charles A. Hunter, Jr., Indianapolis.

INFARCT FOLLOWING BLOOD DONATION

American Association of Blood Banks:

- Four seemingly healthy blood donors had myocardial infarctions within 48 hours after their donations. No reports of this complication were found in the literature. It is hypothesized that syncope, arrhythmia, bradycardia and hypotension adversely affect an already diseased heart. A donor who experiences syncope should not be accepted again.—Dr. John B. Ross, Jacksonville, Fla.
- Donors who give blood for the first or second time are the most likely carriers of the virus of homologous serum hepatitis. A specific screening test is urgently needed.—Dr. John B. Alsever, Southwest Blood Banks, Phoenix.

LIVE-VIRUS VACCINES USED IN RUSSIA

American Public Health Association:

- In Russia each year 20 million persons now receive live attenuated influenza vaccine administered by nasal spray. A live attenuated vaccine administered intradermally has been used to achieve 90 per cent protection against mumps in 35,000 preschool children. Sabin live-virus poliomyelitis vaccine has been administered orally to 12 million school children. A live-virus vaccine against measles is being tested.—Dr. A. A. Smorodintsev, Institute of Experimental Medicine, Leningrad, Russia.

BETATRON ELECTRONS USED TO TREAT CANCER

Radiological Society of North America, Inc.:

- A high-energy electron beam produced by a betatron was used to treat 72 patients with various stages of metastatic breast cancer. Distinct advantages over conventional x-ray treatment were shown in terms of dose distribution in each clinical setting. Favorable results were obtained; the duration of regression was eight months.—Dr. Florence C. H. Chu, Memorial Center for Cancer and Allied Diseases, New York.
- Marked although temporary improvement is achieved in patients with esophageal cancer who receive a course of radiation therapy prior to surgery. The procedure also increases the number of patients on whom surgery can be performed.—Dr. Eugene Bronstein, New York.
- A follow-up of 71,000 women with cancer of the cervix showed that treatment with radium did not produce a higher incidence of leukemogenesis than is present in the general population.—Dr. Norman Simon, Oak Ridge Hospital, Oak Ridge, Tenn.

TREATMENT OF URINARY TRACT INFECTIONS

Seventh annual Symposium on Antibiotics:

- A study of 75 patients treated with demethylchlortetracycline (DECLOMYCIN®) indicates the drug will probably play an important role in the future treatment of urinary tract infections. Patients were given 900 mg. Declomycin daily for six days. Those with acute infections responded more favorably than did those with chronic infections. Serum was taken from 13 patients for a test of antibacterial activity in the blood. Results showed that the drug had three times more activity than did tetracycline.—Dr. Myron S. Roberts, Presbyterian and Babies Hospitals, New York.
- The minimal inhibitory concentration (MIC) values on 104 strains of *Staphylococcus aureus* obtained in a comparative study with other penicillins denote that potassium penicillin-152 inhibits a greater number of penicillin G-resistant *Staph. aureus* organisms than do penicillins O and V.—E. M. E. Morigi, Philadelphia.

FIRST 44A STRAIN STAPHYLOCOCCUS EPIDEMIC

Central Society for Clinical Research:

- Following elimination through a rigid control program of the 80/81 strain of *Staphylococcus*, the most common agent in nursery infections, an epidemic due to the 44A strain has occurred. The 44A strain is relatively common in hospital personnel, but assumes epidemic importance only when the 80/81 strain is absent. This observation offers a preview of future problems in control programs that are directed only against a specific strain.—Dr. Robert E. Windom, University of Texas Southwestern Medical School, Dallas.
- Four electrocardiographic phenotypes, identified by the sequence of intraventricular activation, have been identified in man on the basis of a study of 1,035 persons of heterogeneous racial background. Analysis of the electrocardiographic pedigrees of 45 families, some of which include four generations, suggests that the four phenotypes represent clear-cut, easily recognizable entities suitable for evaluation as hereditary traits. The phenotypes appear in filial generations consistent with the laws of simple Mendelian heredity. Aside from its potential use as a medicolegal tool, this observation, if confirmed, may help establish the normality and abnormality of the electrocardiogram and the misdiagnosis of normal variations through comparison with electrocardiograms of the parents and children of the patients.—Dr. J. Marion Bryant, Bellevue Hospital, New York.

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Source: Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

for those pediatric puzzlers..."A routine urinalysis and blood sugar should be done whenever the possibility of diagnosing diabetes is entertained."*

DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

Symptoms	No. of Patients	Per cent of total group
Polyuria	93	84.5
Polydipsia	89	81.0
Weight loss	47	42.7
Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
Boils	1	0.9
Headache	1	0.9
Abdominal cramps	1	0.9

Adapted from Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.*

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Forensic Medicine

Radiography in Crime Detection

JOSEPH S. PRICE*

Chicago Police Crime Laboratory, Chicago

JOSEPH S. PRICE

For the past two decades or so, x-rays in many forms have been used in various aspects of scientific crime detection. The use of x-ray diffraction and fluorescence to analyze evidence exhibits of unknown composition is considered commonplace procedure in modern methods of scientific crime detection. However, the oldest and simplest of all the technics employing radiation has been more or less neglected. This is the field of shadowgraphy. The extent of the spectrum that can be employed in this application of radiation is rather wide. Radioactive sources such as cobalt can be used to obtain extremely short wavelength radiation, while very long wavelength radiation can be obtained through the use of specially constructed tubes capable of transmitting radiation generated by potentials as low as 1 kv.

In the light of the wide latitude afforded in this means of examination, I believe that there is a great potential for the use of x-rays in the forensic sciences. I also believe that a better understanding of available instruments and of their applications can promote a widespread use of this technic. It is with these thoughts in mind that I wish to share my experiences in this branch of science.

Objections to Use of Radiography

Since I intend to make this paper as basic as possible, some common problems concerning this field must be discussed first. It has been noted that a reluctance to the use of x-ray technics does arise and that most of the objections are due chiefly to the following sources.

Undoubtedly, the first concern is the cost of the equipment. However, in comparison with the cost of other pieces of equipment that

(Continued on page A-37)

*Sergeant, Chicago Police Crime Laboratory, Chicago, Illinois.

Presented at the eleventh annual meeting of the American Academy of Forensic Sciences, Chicago, Illinois.

TABLE 1

UNITS USED IN RADIOGRAPHIC EXPERIMENTS

TYPE OF UNIT	CONTROL	KILOVOLTAGE	WAVELENGTH*
General Electric portable unit	Three steps	65	0.189
		70	0.176
		75	0.164
Universal X-ray grenz ray unit	Continuous	7.5	1.70
		15.0	0.81
Philips microradiographic unit	Continuous	1.0	12.35
		5.0	2.45

*Calculations of wavelengths were made with the formula Lambda-Å $= \frac{12.35}{KVP}$. Å is Ångström unit; KVP is kilovolt peak, and 12.35 is a constant.

are deemed essential in a well-functioning laboratory, x-ray equipment is not out of the range of normal expenditures.

Another factor concerning the use of radiography is the skill required to operate such equipment. It is here that we are generally faced by some awesome beliefs regarding dangers and technical difficulties. Insofar as dangerous conditions are concerned, strict adherence to precautionary measures, as outlined in the manuals accompanying the equipment, is adequate. The physics and photography involved in the operation of x-ray equipment are not unlike those which we find in normal photographic work. Exposure time, subject distance and density, proper films, developers and the skill required in normal photography are applicable with slight modifications. Probably the most advantageous difference is that no lens is used in radiography, nor does one have to depend on the reflective property of light. Thus, it can be said that this technic is far simpler than is that of ordinary photography.

Radiographic Experiments

At this point, one can visualize the necessity of a certain amount of experimental work in the use of radiography in order to achieve optimum results. To illustrate what a powerful tool the x-ray really is, I selected from our collection of radiographs various types of subject matter made under diversified conditions.

Three machines were used in our experiments: a model F-4 portable unit made by the General Electric Company, a grenz ray unit made by Universal X-ray Products, Inc., and a microradiographic unit manufactured by North American Philips Co., Inc. The General Electric machine produces x-rays in an intermediate range, which is generally classified as a hard type of radiation. The Universal and Philips units produce so-called soft radiation. Table 1 shows the range of these instruments, as indicated by their manufacturers, in regard to kilovoltage available, manner of control, and wavelength in Ångström units.

In this work, especially when using soft radiation, two factors become increasingly important: (1) the distance between the x-ray tube and the subject matter and (2) the composition of the window of the x-ray tube. The latter is the more important consideration, for it is in the window that we find the characteristics which limit the transmission of energy. Within the tube, radiation of a wide range of wavelengths can be generated both theoretically and practically.

This theory was tested by actual experiment with our General Electric F-4 unit. After examination of the electric circuitry of the apparatus, it was concluded that it was possible, with very simple alteration, to insert in the primary circuit of the high-tension transformer a proper-sized variac to control the high-voltage output in the unit. It was found, how-

(Continued on page A-38)

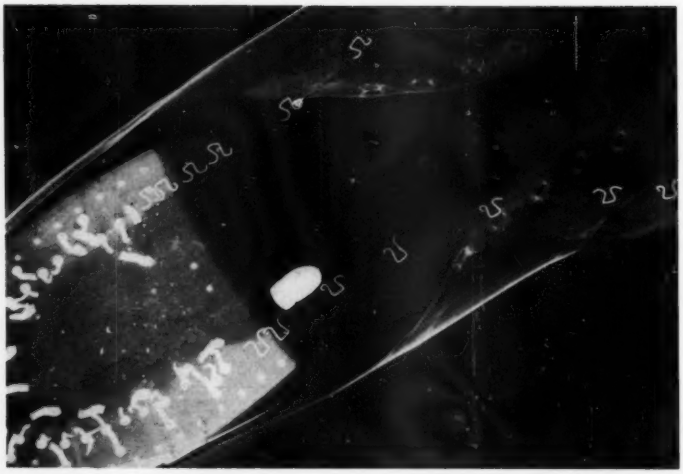

FIGURE 1. Radiograph of a bullet in a shoe. The bullet entered the victim's leg near the ankle, coursed through the foot, and became imbedded in the sole of the shoe. Coagulated blood resulting from profuse bleeding concealed the position of the bullet. The information revealed by this x-ray permitted the bullet to be removed with minimal mutilation and the shoe to be returned to the owner with only a little damage.

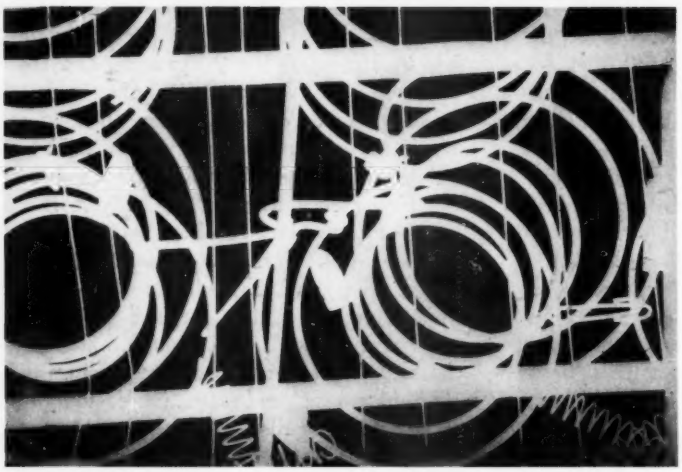

FIGURE 2. Radiograph showing bullets in a car seat. In this case, a fluoroscope was used initially to locate the pellets, and the radiograph was made later.

ever, that in spite of the electric accomplishment we were still unable to get a soft radiation out of the tube. The limiting factor was the nature of the window material, which was such that it filtered out the soft radiation and permitted the passage of only the harder radiation. This problem can be solved by installing a tube which has the necessary properties in the window. However, this installation is not without its technical difficulties. The ideal situation would undoubtedly be one in which the subject matter could be placed inside the tube itself. This situation is similar to that encountered in the electron microscope.

Since the nature of the exhibits does not permit an ideal situation, it is necessary to resort to the next best manner of operation—the utilization of equipment provided with controls and tubes with appropriate windows. Both the Universal and Philips units are equipped with tubes of these specifications, having extremely thin beryllium windows. According to manufacturers' data, the Philips tube is provided with a beryllium window 50 μ in thickness.

In order to obtain optimum results with printed matter, it was necessary to construct

(Continued on page A-40)

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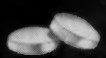

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Riker

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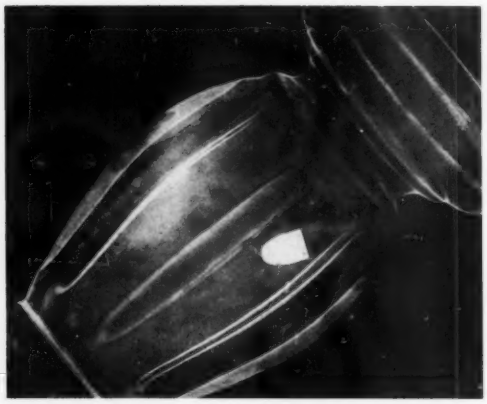

FIGURE 3. The use of radiography in this case permitted a bullet to be removed from a chair leg with minimal damage to both the chair leg and the bullet.

a vacuum cassette. With this device, it was possible to have intimate contact between the subject matter and the film during the exposure. This technic eliminates undesirable effects such as enlargement, distortions and diffusions. The cassette was very simple to construct. It consisted of a sealed box about 15 by 10 by 3 in. in over-all measurement. The top of the box was then drilled with a large number of small holes, and provision was made at the side to accommodate a hose from a vacuum cleaner. To provide a control for the amount of vacuum, it was found desirable to use a suitable variac in conjunction with the vacuum cleaner. This control of vacuum was to prevent the subject matter from being drawn into the holes of the cassette by too great a vacuum.

The steps in using this device consist of placing a sheet of film on top of the cassette while a small or sufficient amount of vacuum is being drawn; the subject matter is then placed on top of the film. Finally, a sheet of vinyl plastic is placed over the setup, which is then ready for exposure to radiation.

Another deterrent to success in low-voltage radiation is the air absorption factor. When using potentials of 5 kv or less, loss of air absorption became noticeably greater in the column between the tube and film. To compensate for the losses incurred, we tried using higher current intensities and longer exposure times. When this proved to be neither a satisfactory nor a practical solution to the problem, we tried another technic which consisted of constructing a chamber with which it was possible to condition the column between the x-ray tube and subject matter. This chamber consisted of a brass tube about 6 in. in diameter and 18 in. long. One end was fitted to the x-ray tube holder and the other end could be sealed. An outlet also was provided at the side of the chamber, permitting the chamber to be evacuated or filled with a gas. Either hydrogen or helium can be used as the low-absorption gas in the column. The latter was chosen because of its safety features, although it is not of a lower atomic weight.

The radiographs made with the aid of this technic were of a more revealing and desirable nature than were those made under similar conditions without the use of the chamber. This suggested that further use of this media control within the column would attain more desirable results.

The Philips microradiographic unit, a small lightweight instrument, was designed for examining small specimens, which are placed in a vacuum chamber along with the film. This arrangement permits differences in density to be clearly shown in the structure of the material, thereby eliminating the need for staining. A disadvantage to this method, however, is that no initial magnification is obtained. The enlargement depends directly on the resolution of the film. Fine-grain films are available for this purpose, with resolutions up to 0.5 μ; however, films of this type were not used in any of the work presented here.

Subject Matter and Objectives of Examination

It has proved profitable to study evidence exhibits by means of x-rays for several reasons. With x-rays, one does not have to contend with several factors that are of a limiting nature in conventional photography. The prime requisite in x-ray examinations is to achieve sufficient difference in density between the surrounding media and the object of the

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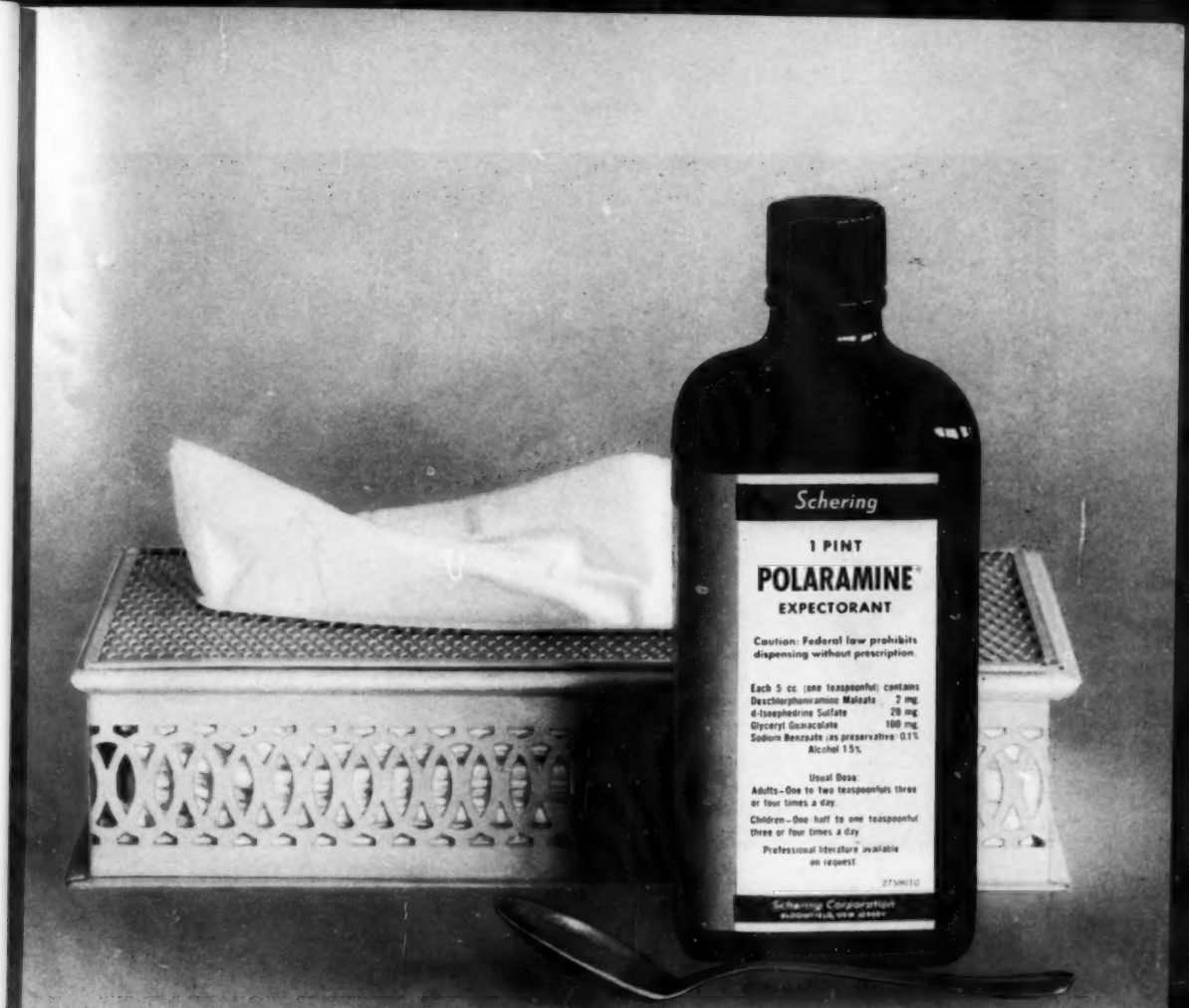
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FIGURE 4. A biologic specimen in which the hemal canals and the spines of the dogfish shark are clearly shown. These minute structures would not be visible in ordinary photography.

search. The portion of the radiograph exhibiting light areas is indicative of the presence of a radiation-absorbing material in the path of the x-ray beam. In contrast to this simplicity, let us note the involvement and limitations of ordinary photography. The requirements for this technic demand that the subject matter be on the surface of the sustaining media and that the media be transparent. Furthermore, there must be differences in shape which cause shadows or color differences before satisfactory results can be obtained.

Illustrations accompanying this paper are numbered according to the order of increasing wavelengths used in the radiographs and of the decreasing density of the subject matter. Sometimes enlargement is used to accentuate the object of study. Radiographic representation has been strictly maintained with respect to the light and the dark areas which depict absorption.

Summary

Although considerable time and effort have been involved in this project, we feel that it is merely a beginning in the utilization of x-rays in forensic science.

There is no doubt that similar situations or circumstances have confronted others in this field. Perhaps the technics which we have introduced will stimulate others to participate and advance in this field of endeavor.

At the inception of our project, we had only the General Electric instrument with which to work. The results we achieved in the intermediate range, which permits penetration of dense materials, indicated the possibility of other ranges that could be useful. We therefore entered on a research project and acquired two other units, namely, the Universal and Philips instruments. Both of these ma-

(Continued on page A-44)

VERSATILE FURACIN

effective by intrapleural instillation[1]

the situation: Four-month-old infant with staphylococcal pneumonia and empyema resistant to most antibiotics was allergic to antibiotic chosen after sensitivity tests. Thoracentesis produced 30-40 cc. of creamy, purulent fluid. Organism was Staphylococcus aureus, coagulase positive.

then Furacin was instilled: 0.2% Solution was diluted equally with physiologic saline and 10 cc. of mixture instilled twice daily into pleural space, with suction catheter clamped off for 1 hour. Fluid almost immediately became thinner and less viscous. Twenty-four hours later infant was less irritable, voluntarily started taking food. Instillations stopped. FURADANTIN® Oral Suspension prescribed. Recovery uneventful.

1. Perkins, J. L.: Kansas State M. J. (to be published).

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chines were designed to produce soft radiation, which is necessary in the examination of low-density materials.

Having had the opportunity to test and compare the three instruments—the General Electric, the Universal and the Philips—we found that each unit had a limited area of effective operation. Much of our work had to do with trying to modify the standard x-ray units to meet specifications which would be applicable to our type of work.

As a result of our experiments, we believe that an ideal soft x-ray unit would conform to the following specifications. The voltage source should be capable of delivering 5 to 15 kv and 5 to 10 ma. of current, the control of which is to be in a continuous and variable manner. The tube should have a window of a material and construction which would permit transmission of the low-energy radiation necessary and which also would be capable of covering an 8 by 10 in. film at a distance of approximately 30 in.

The ideal instrument would have operating features somewhat similar to those of the electron microscope. Of course, we are limited in this regard because of the usual size of the specimens in our casework.

The Philips unit gives excellent results at its maximal output of 4 to 5 kv. The Universal unit, with a range of 7 to 15 kv, came closest to meeting the ideal specifications.

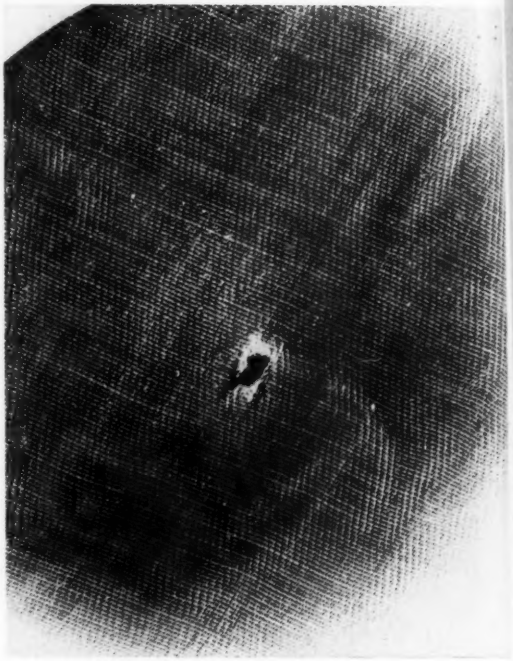
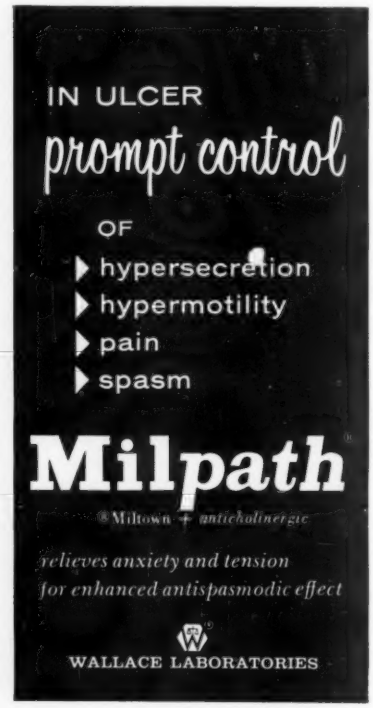


FIGURE 5. Bullet hole in denim trousers. In this case, the victim received a flesh wound from the bullet, which was fired at him during an attempted burglary. The doctor who treated the wound notified the police that he was treating an accident case.

Suspicious of the circumstances, the police made this x-ray, which showed heavy deposits of dense material, represented by the light areas at the proximity of the hole. Spectrographic examination revealed that the material consisted chiefly of lead. Further examination showed similarities in the composition of the material and the bullet. The injured man later confessed to the crime.

ACKNOWLEDGMENTS

I am deeply indebted to the following for technical assistance and for the extended use of the equipment needed to conduct these experiments: Dr. Herbert Pollack, radiologist, Mr. Joseph Heger of C. H. Stoelting Company, Universal X-Ray Products, Inc., North American Philips Co., Inc., and members of the Chicago Police Crime Detection Laboratory.



Radiology FOR PRACTICING PHYSICIANS

A Russian Interlude

PAUL C. HODGES*

I AM not an expert on Russia. It is embarrassing to admit the fact, because by the rules of the game I should be. I have read Harper, Vernadsky, Kennan, Pasternak, Stevenson, Moorehead, Gunther, Berdyaev, Rama Rau, and De Caulaincourt,[1-10] together with translations of Tolstoi, Chekhov, Pushkin, etc. Thanks to the devoted efforts of my Russian teacher Raissa Palyi, I also have struggled through some hundreds of pages of grammar[11] and simplified versions of certain of the stories of Pushkin and Lermontov[12] in Russian. Furthermore, from June 12 to July 4, 1959 (after Adlai and before Dick), I traveled as one of Intourist's hundreds of summer visitors from Leningrad to Petrodvorets, Pushkin, Minsk, Kiev, Odessa, Yalta, Alupka, Novorossisk, Sochi, Adler, Gagra, Gorki, Tbilisi, Mtskheta, Pasauri, Moscow and Zagorsk. I subsisted on caviar, vodka, cucumbers, Kiev cutlet, beef stroganoff, exotic breads and Crimean wines. I was entertained by superb ballet, opera, orchestra and circuses and escorted to unbelievably beautiful palaces, parks, fountains, Black Sea coastal areas, and the snow-capped Caucasus Mountains.

By current practice, 21 days spent at these activities should qualify me to advise my friends, congressmen, senators and even the President on every phase of Russian life, economy and politics, but, unfortunately, it has not worked that way with me. The only advice I feel capable of giving anyone is this: By all means, do plan to visit Russia; however, if it is at all possible, go in May or September, when Moscow's fabulous opera, ballet and puppet theater are not closed and when Intourist is not completely bogged down with summer visitors. Furthermore, if you are a physician and expect to see as much as pos-

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

sible of Russian medicine, some sort of government sponsorship might be helpful.

It was my intention to visit physicians, particularly radiologists, in each of the seven major cities on my route. Correspondence relative to this objective began many weeks prior to my departure from New York. It soon became clear, however, that in this, as in all other arrangements for foreign travelers, actual contact would have to be through Intourist, an agency reasonably competent to arrange for hotels, transportation and entertainment but inept in medical matters. Sanatoriums and spas in the Black Sea region were right down their alley, and, presumably, we could have visited as many of these as we wished. However, only by making first-rate nuisances of ourselves did we get into three hospitals, and one of these was included only with the cordial and effective assistance of Dr. D. E. Langdon of the United States Embassy in Moscow. We were convinced, however, that the difficulty was due to Intourist fumbling rather than to a policy of exclusion. Whenever we did get through to physicians, we always encountered unfailing cordiality and frankness.

I have slipped from "I" to "we" not carelessly or by editorial prerogative, but because I was accompanied by two charming American women, my colleague Professor Henrietta Herbolsheimer and her mother Mrs. Catherine Herbolsheimer of Peru, Illinois, who in her eighty-first year is a spry and observant world traveler. They attended medical meetings in Scotland and France; I attended a congress in Germany, and we joined forces for the swing through Denmark, Sweden and Russia. Dr. Herbolsheimer is one of Mrs. Palyi's abler students; while her command of spoken and written Russian is far from perfect, it is astonishingly effective and her obvious professional ability and unusually attractive personality opened doors and hearts to us. Furthermore, as the illustrations testify, she is a gifted and indefatigable photographer. Mrs. Herbolsheimer, who had feared she would slow us down on what obviously would be a strenuous three weeks, proved to be a practical asset as well as a congenial companion. On trains, planes and ships, in hotels, theaters and circuses, Russian men and women, marveling that one so ripe in years would venture so far from home, helped her and, incidentally, us in innumerable ways. Our social contacts were made largely at night, when our guides were off duty and we were free to wander as we wished through parks, along city streets, or along esplanades in the Black Sea region. Here, too, Mrs. Herbolsheimer's presence paid off. She was attracted to children and they to her, and the usual gambit was to inquire their names and then their ages. This usually brought the parents into the conversation and by the time we were able to convince them that they had not misunderstood us and that she was in fact 81 years old the conversational ice had been broken thoroughly.

As many travelers have observed, Russians are extremely fond of children; however, instead of being spoiled by attention and a disproportionate share of such clothing as the family can afford, the children are by our standards amazingly well behaved. We saw hundreds of them and talked with scores, and yet only one of us saw a single instance (and that a mild one) of a whining child and a scolding parent. Perhaps we should try to arrange to trade American hybrid seed corn for the Russian formula for amiable parent-child relationships.

Public Health Service Medical Tours

A five man group from the United States Public Health Service visited Russia February 27 to March 28, 1956. Two of them, Dr. Michael B. Shimkin and Dr. Karl F. Meyer, later came to the University of Chicago, showing us their slides and telling their findings. From their formal report,[13] we prepared a map of their route (figure 1), which took them from Leningrad and Moscow to Kiev, Karkov, Rostov, and the famous primate colony at Sukhumi at the extreme southeast end of the Black Sea.

In the following year a second five man group, led by the former surgeon-general Dr. Thomas Parran, also visited Russia. Their itinerary started, of course, with Moscow and Leningrad and included Kuibyshev, Ufa,

FIGURE 1. Route of the American Medical Mission on Microbiology and Epidemiology to the Union of Soviet Socialist Republics, February 27 to March 28, 1956.

FIGURE 2. Route of the United States Public Health Service Mission, August 13 to September 14, 1957. In spite of the extensiveness of the trip, it included only a portion of the western fourth of the country. The route of Dr. Hodges and party (see figure 3) is shown at the left.

FIGURE 3. Route followed by Dr. Hodges and party, June 12 to July 4, 1959. This route included Odessa, the Crimea and the Caucasus, which were not visited by either of the two medical missions.

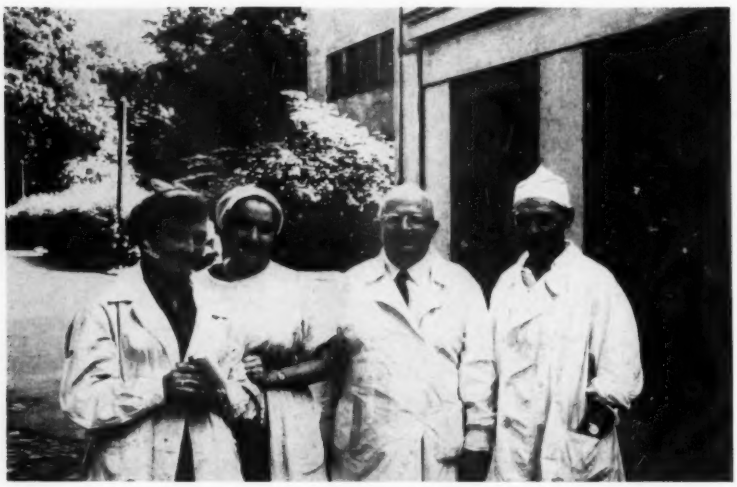


FIGURE 4. The First Medical Institute, Leningrad. *Left to right.* Intourist interpreter; Dr. Feyrusa Mursalova, assistant to Professor F. G. Uglov, chairman of surgery; Dr. Hodges; and Professor Uglov.

Tashkent, Samarkand, Stalinabad, Frunze and Alma-Ata, which stands at the boundary between European and Asiatic Russia (figure 2). Their trip, in late August and early September 1957, has been the subject of numerous articles in medical journals and the newspapers; this year, it appeared as a report[14] of the Public Health Service.

Our Route

Our route (figure 3) corresponded roughly with that of the first Public Health Service group, except that we included Odessa, Yalta and Sochi, on the north coast of the Black Sea, and Tbilisi, which lies in the foothills of the Caucasus halfway to the Caspian Sea and is the capital of the Georgian Republic. We were not able to visit the important microbiologic station at Sukhumi, which includes a large colony of monkeys, some in the sixth generation.

Leningrad—Leningrad, former capital of the czars, and nearby Petrodvorets and Pushkin have unique beauty and historical interest, which we enjoyed to the limit. Nevertheless, from the hour of our arrival in Leningrad we lost no opportunity to impress on Intourist officials the fact that a principal purpose of our visit was to see Russian medicine and particularly Professor Fedor G. Uglov, chairman of surgery of the First Medical Institute (figure 4). On a recent trip to the United States, Professor Uglov had been entertained by Dr. Charles W. Mayo, and Miss Sylvia Covet, executive editor of POSTGRADUATE MEDICINE, thoughtfully had provided me with a letter of introduction. Eventually, we broke down bureaucratic lethargy and did get to the Institute. Once there, we were in the hands of friends and could even have done without our ubiquitous Intourist interpreter, because most of our conversations were carried on in English, German and our smattering of Russian.

Until recently, medicine has carried a rather low priority in the Soviet scheme of things, not because of any lack of recognition of its importance, I believe, but because there have been so many more pressing demands on money and manpower. The Institute, like the others we visited subsequently, is housed in old, inadequate quarters. Laboratories, operating rooms and patients' wards are crowded, and, unlike the marble palaces called sanatoriums, presently to be described, the hospital and Institute buildings are old and anything but elegant in appearance. However, they were clean and they hummed with cheerful activity. There are plans for a modern plant, which undoubtedly will be built soon.

In addition to his very considerable staff of associates and assistants, Professor Uglov

FIGURE 5. Department of Radiology, First Medical Institute, Leningrad. *Left to right.* Professor D. G. Rochlin, chairman of roentgenology; Dr. Hodges; Dr. Sadvornova, assistant to Professor Rochlin.

has numerous students, many of whom we saw at work on experimental mammalian thoracic and cardiac surgery. In the operating rooms we saw patients undergoing similar types of surgery, and in the wards we saw patients recovering from these operations.

Radiology is in charge of Professor D. G. Rochlin and his associate Dr. Sadvornova (figure 5). This department does the routine clinical radiology for the Institute, carries on investigation and teaching, and maintains a museum of osteology. The x-ray equipment is old but in good working order and the x-ray films, of which I saw many, were of good quality.

The maintenance of good and uniform quality in the manufacturing of x-ray films, screens and tubes is a revealing test of a nation's technological capacity, and I am informed that throughout the Union of Soviet Socialist Republics practically all films and screens and most tubes that are used are made in Russia.

Kiev—In Kiev, capital of the Ukraine, the shoe was on the other foot, because we were offered an opportunity to visit a gynecologic hospital. At the last moment, however, we turned it down when there was an unanticipated opportunity to visit a collective farm. Kiev did, however, teach us something about the efficiency of the Soviet Public Health Service. When we applied to the dining room stewardess of the Ukraine Hotel for box lunches to take on the night train from Kiev to Odessa, we were informed that Public Health regulations specified the types of food that could safely be dispensed in unrefrigerated lunch boxes during the summer months. Furthermore, on the train itself, which was of ancient and uncomfortable design, our insect repel-

FIGURE 6. Filatov Institute of Eye Diseases and Tissue Therapy, Odessa.

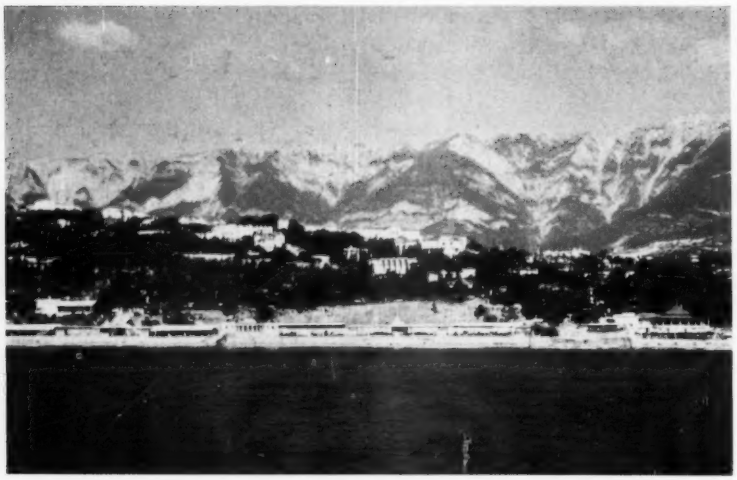


FIGURE 7. View of Yalta from the Black Sea. Most of the buildings are sanatoriums; some are former palaces of the czars and the nobility. Most of these buildings have been constructed since the revolution, particularly since the end of World War II.

lents remained unopened, because no vermin whatever were encountered.

Odessa—By great good fortune, our visit to the world-famous Filatov Institute of Eye Diseases and Tissue Therapy (figure 6) preceded by a few days an ophthalmologic congress. In anticipation of the congress, dozens of patients with corneal transplants had been brought back to the Institute. The director, Professor N. A. Puchkovskaya, a friendly, obviously capable woman, received us most cordially and introduced us to her radiologist, Dr. Panfilova, also a woman. Professor Puchkovskaya speaks and understands English, and Dr. Panfilova speaks German and understands English, so we had little need for our Intourist interpreter.

The late Vladimir Filatov in 1936 established as the Ukrainian Research Institute for Eye Diseases the institution which now bears his name. After the end of World War II, he rebuilt it on the ruins. The present plant includes 16 laboratories and 300 patient beds. Dr. Panfilova discussed with me the facilities and work of her x-ray department, which includes equipment of Russian, American and European make and in which are done all types of radiologic work in addition to the localization of foreign bodies in the eye. She was conversant with American and European practice, and she had developed certain ingenious modifications of her own. It was her intention and mine that I visit her laboratory, but when the parade of corneal transplant cases began I could not tear myself away.

In his little monograph, Filatov[15] made no claim to priority in surgical transplantation of the cornea, and his successors are equally modest. However, the Filatov school has been diligent and skillful in this field and Soviet law expedites their work. Unlike the American ophthalmologic surgeon, who must resort to eye banks or wait for the death of someone who has agreed to the use of his eyes after his death, the Russian physician receives eyes on request from the nearest undertaker without the consent or even the notification of relatives. Corneal opacities encountered by the Odessa group seldom result from trachoma; they more commonly follow smallpox, burns, explosions, chemical injury or various types of mechanical injury. We saw dozens of patients whose vision had been restored in whole or in part by corneal grafts on one or both eyes. We were informed that whereas the first attempt usually succeeds sometimes it is necessary to repeat the operation up to five times before a "take" is accomplished. The factors making for compatibility or incompatibility between the graft and the recipient are now under investigation at the Institute.

FIGURE 8. Chauika Sanatorium, Sochi. Hundreds of millions of rubles have been expended on scores of such structures, some of which are even more elaborate than this one. Such extravagance is now deplored by the Russians, and current programs call for simpler, more functional buildings.

Yalta—The overnight vessel from Odessa to Yalta is comfortable and interesting, and the beauty of the Black Sea and the Crimea is as breath-taking as has been claimed by travelers beginning with the ancient Greeks who traded art work for grain, down through Mark Twain, to modern travel booklets.[16] Formerly the czar, his relatives and many of the nobility maintained palaces there, and there were a few resort hotels in this area because it was esteemed as a restful refuge from the rigors of north Russian winters. Under Lenin's first Commissar of Public Health N. A. Semashko,[17-19] these buildings were expropriated, and with the years many more have been built at Yalta (figure 7) and elsewhere, particularly along the Black Sea coast. Thus, in 1957 there were more than 2000 sanatoriums, with facilities for almost 300,000 patients, and 900 holiday homes housing about 160,000 guests. Ownership is divided among central government, provincial governments, trade unions, farm groups, etc., and apparently there are wide variations in the criteria for eligibility for entrance. Some patients and vacationers appear to be selected on the basis of performance in industry, with the union or other public agency paying two-thirds and the individual paying one-third of the cost. Most of the buildings which we saw lack elevators and are not suitable for and apparently are not patronized by patients who are unable to negotiate formidable flights of steps.

Beyond the harbor at Yalta, the coast is an almost continuous bathing beach; buses are provided to bring patients to the sea, and small vessels are available to take them along the coast from one beach to another. Regardless of what one may think of the clinical value of sea bathing, mud packs and sulfur water baths, no one will doubt the psychologic advantages of two or three weeks of relaxation in warm, beautiful surroundings free of the crowded housing and dietary restrictions still inherent in workaday Russian life.

For physicians, a visit to the home of the playwright Chekhov is of particular interest, because he was a physician and continued a limited practice in his Yalta home, where he entertained many of the most famous European theatrical and musical people.

Sochi—Another fine sea trip took us from Yalta to Sochi. We passed en route the entrance to the Sea of Azov and stopped briefly at Novorossisk. The seacoast above and below Sochi is dotted with sanatoriums, and motor roads lead up into the coastal range of the Caucasus. We were quartered in Sochi at a palatial sanatorium called Chauika (figure 8), which is the Russian for sea gull; we ate some meals at the patients' mess and we had an unusual opportunity to observe the work-

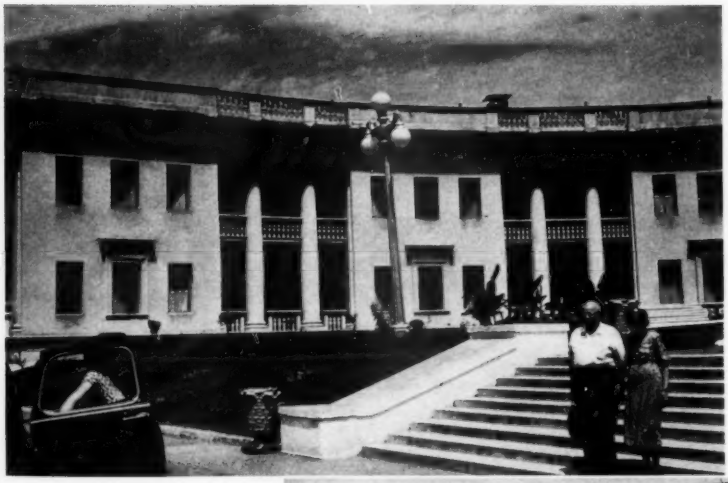


FIGURE 9. Matsesta sulfur springs spa, Sochi. This enormous palatial building (see also figure 10) has no resident patients. Fleets of buses bring patients from residential sanatoriums to bathe in the sulfur springs, inhale their fumes, or receive the water by irrigation. This is all by the prescription of physicians who appear to take their work seriously with no trace of a tongue-in-cheek attitude.

Descending the steps with Dr. Hodges is Mrs. Herbolsheimer; at the door of the Russian-made car is the Intourist interpreter.

FIGURE 10. Main entrance of Matsesta spa. Women gardeners are at work on intricate floral designs which abound throughout the area and which have been likened to botanical embroidery.

ing of one of the larger sanatoriums. It rose in terraces on a steep hillside and there were no elevators. Inside the palatial exterior the rooms were pleasant but modest; food was plentiful and of good quality, and the patients apparently were not very ill. Another sanatorium a few steps away had a funicular railway that carried all comers down and up the steep hillside under the main road to and from a large bathing beach provided with piers, showers, toilets and sun-bathing porches.

Buses take patients on day-long sightseeing trips down to Gagra and beyond and up through the gorge of a mountain stream to beautiful Lake Ritsa. They take them also to Matsesta (figures 9 and 10), the sulfur springs spa, for prescribed applications of the water so rich in hydrogen sulfide that bus drivers, if necessary, could find the place by following their noses.

In Leningrad and Moscow even the best hotels are meagerly supplied with citrus and other fruits, berries, tomatoes and similar garden stuff; presumably, such items are rare indeed on the tables of householders. In the Black Sea region, however, large farms and hothouses are devoted exclusively to the raising of such produce for the sanatoriums.

FIGURE 11. *Left.* Professor E. A. Vasyukova, director of the Institute of Experimental Endocrinology, Moscow. *Right.* Dr. N. I. Perevakchikova, worker at the Institute of Experimental Pathology and Cancer Therapy.

Tbilisi—Capital of the Georgian Republic, Tbilisi is reached by an all-day ride on a first-class electrified train that winds up the valley of the Puonu River through Gorki, which is Stalin's birthplace, and thence along the Kura River. Our medical contact in Tbilisi was to have been Professor N. A. Dzhavakhishvili, who was a member of the group that visited us in 1957, but we were unable to get through to her or to anyone in the department of anatomy in the Institute of the Georgian Academy of Sciences. We did, however, observe at first hand the functioning of a Soviet first-aid team. Driving along the Georgian military highway as we were returning from an all-day trip into the Caucasus, we came on a truck accident in which several riders had been injured, one seriously. Tempted at first to offer our services, we abstained when we saw how smoothly other truck drivers were transferring the injured to a Tbilisi-bound vehicle. Apparently still another truck had been dispatched with a message, because a few minutes later as we passed through a village we saw the improvised ambulance parked at a little roadside building while white-robed attendants carried the injured inside.

Moscow—The trip from Tbilisi to Moscow was by one of the excellent new Russian jet planes, and en route we had the rare experience of seeing the snow-capped peaks of the high Caucasus thrusting up through a sea of clouds, which the day before had obscured them from us on the military highway.

We had most carefully tried to make advance arrangements for medical visits in Moscow. Letters had passed between us and Pro-

FIGURE 12. Institute of Oncology, Moscow. *Left to right.* Professor A. N. Novikov, director; Dr. Eugene A. Lichtenstein, radiologist; Dr. Vera V. Gordilova, deputy director; Dr. Henrietta Herbolsheimer, associate professor of medicine, University of Chicago.

FIGURE 13. Network of oncologic dispensaries of the Russian Soviet Federated Socialist Republic. This photograph was furnished through the courtesy of Professor Novikov.

fessor F. Krotkov, Academy of Medicine; Dr. V. N. Zhdanov, Deputy Minister of Health; Professor M. N. Fateyva, a woman radiologist who had visited us in Chicago in 1957; and Professor D. Venedektov, Ministry of Public Health. Unfortunately, by the time we reached Moscow some of these physicians were themselves patients in the hospital and others were on vacation. The Moscow office of Intourist offered little help in arranging appointments for us. Finally, almost on the eve of our departure, we did get through to Professor Venedektov, after which our troubles were at an end. I know from American friends resident in Moscow that the professor is a terribly busy man, and so I appreciate deeply the graciousness with which he received us, explaining the working of his Ministry and making arrangements for our visits on the following day.

We went first to the Institute of Experimental Endocrinology (figure 11), the director of which, Professor E. A. Vasyukova, had headed the delegation of women physicians who visited the United States in 1957. She also had kindly invited another of the visitors to America, Dr. Perevakchikova, a worker in the Institute of Experimental Pathology and Cancer Therapy of the Academy of Medical Sciences. This joyous meeting of old friends made up for the frustrations of the preceding days, and Professor Venedektov had prepared the way so thoroughly that when we went on to the Institute of Oncology (figure 12), Professor A. N. Novikov and his staff received us with such warmth that it seemed as though we were not meeting for the first time. His radiologist Dr. Eugene A. Lichtenstein speaks fluent idiomatic English, so questions and answers presented no problem and there was no occasion to practice our meager Russian.

This Institute is the chief Soviet cancer institution and directs all cancer work throughout the Russian Soviet Federated Socialist Republic (figure 13). The Moscow unit is concerned primarily with therapy but does investigation as well, having for this purpose departments of physiology, biochemistry, virology and experimental therapy. Clinical work is divided into departments of surgery, radiology, otolaryngology and gynecology; a department of proctology is under construction. Diagnostic x-ray equipment is of Russian, American and European make; there is a 400 gm. cobalt-60 applicator, and a cesium applicator is under construction.

As in the other institutions we visited, members of the staff were serious, competent, hard-working and well informed. They were modest about their own accomplishments without any trace of the bombast which flourishes under questioning by public relations officers apparently not only in Russia and the United States

but throughout the world. Speaking through press agents, individual physicians sometimes make preposterous claims which grow as they are repeated by uninformed listeners. We encountered talk of this sort among the young, relatively uneducated men and women who served as our drivers and sometimes our guides, but not once did we find it at the Ministry of Health, the First Medical Institute in Leningrad, the Filatov Institute in Odessa, or the Institutes of Endocrinology and of Oncology in Moscow.

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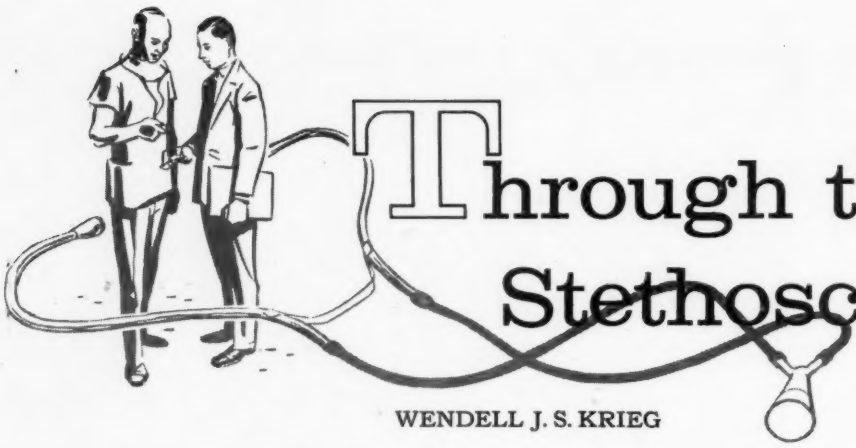

Through the Stethoscope

WENDELL J. S. KRIEG

Letters to a Medical Student

My dear son:

You are understandably dismayed by the mass of counsel in these letters, some of which seems contradictory. I can say with Walt Whitman, "Very well, then, I contradict myself"; or with Emerson, "A foolish consistency is the hobgoblin of petty minds." But you do press me for a succinct life philosophy. Formulating an answer has been an interesting mental exercise, and I have devised a strictly operational, pragmatic philosophy for a cosmopolitan modern man, which I think cannot be punctured.

A man wants to achieve security and happiness and to make a contribution to society.

A. Security is of several sorts
   1. Earning power
      a. Income from work or on retirement from active work; resources of cash, property or investment
      b. Income from skills, abilities and training
   2. Position
      a. Personal and family safety (which nowadays depends ultimately on the country in which one resides)
      b. Reputation, personality, respect, attainment

B. Happiness, which has two aspects
   1. Enjoyment, which is a product of intensity times duration (this measured in hours of the 24 and years of one's life)
   2. Satisfaction; self-realization (also a product of intensity and duration)

C. Service to society
   1. For the professor, the increase and dissemination of knowledge plus the number of lives he can influence for the better

I have dealt mostly with security and service to society. Happiness deserves serious consideration; there also are unconsidered factors, one of which is esthetic enjoyment.

Don't neglect beauty. In the United States of America, esthetic experience, except for the contemplation of the permutations and combinations of the female face and figure, is left to women, although retired gentlemen can pursue it to a limited extent in gardening and painting. A mature man in a profession who admits to experiencing the esthetic afflatus is vaguely suspected of homosexual tendencies, and certainly could not be relied on for an appointment of any importance. Especially in the financial professions he had best maintain a ranine immobility of facies, if he wishes to be counted a solid man. It seems strange that there should be such an apotheosis of the absence of so valuable a quality as emotional

(Continued on page A-78)

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With a documented record of safety not matched by any other drug of comparable action, scope and efficacy.

And a therapeutic effect of rapid onset, lasting up to 72 hours.

HP* ACTHAR® *Gel* is fluid at room temperature and as convenient to inject as any other aqueous preparation.

HP* ACTHAR® *Gel* is the Armour Pharmaceutical Company brand of Purified Repository Corticotropin (ACTH).

Available in 5 cc. vials of 20, 40, 80 U.S.P. Units/cc. Also in a disposable syringe form, in a potency of 40 U.S.P. Units.

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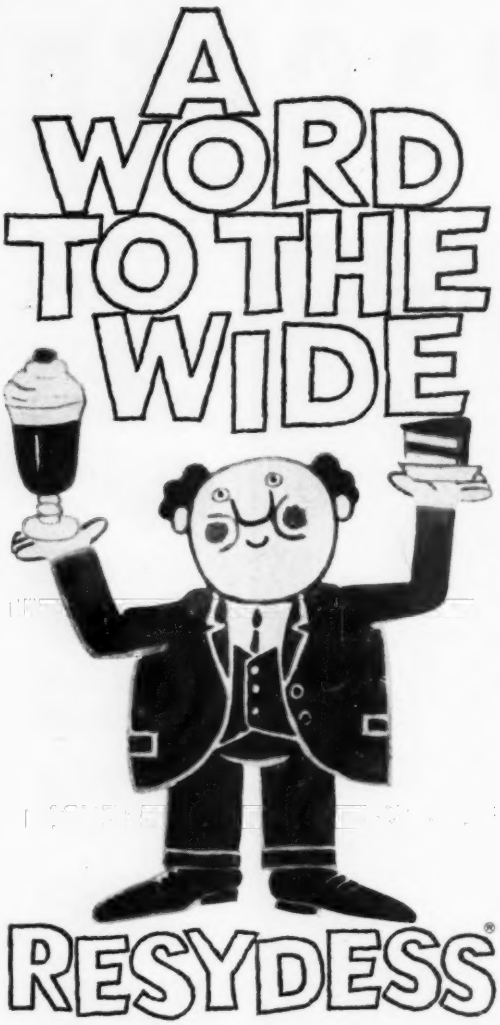

The minimal-dosage RESYDESS regimen brings freedom to the slave of excessive appetite. And the tandem action of the ingredients calms the tense heavyweight while keeping him alert and cooperative.

RESYDESS helps trim the obese problem patient to proper weight—and keeps him there. Try it in overweight patients who have not responded to other medications.

Send for a trial clinical supply.

Each tablet contains
Reserpine.....0.075 mg.
d1-Desoxyephedrine HC1.....8.0 mg.
Bottles of 100 and 1000.

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receptivity, but it is so. I say apotheosis advisedly, as the great god is money; and imperturbability—that is, unresponsiveness—seems to indicate dependability.

Yet some men make the pursuit and expression of beauty their main goal in life, and if they can capture a bit of it on a canvas or in a musical score, they are satisfied. They are some of the best men. Their names are known, and their works live after the safeplayers and the disdainers are gone. If this experience means that much to such men, it may be worth your time to investigate it. The happy thing about it is that beauty gives pleasure. Many men's pursuit of beauty is exhausted in the attainment of a sexual object. Then the account is transferred to this person, who operates it by proxy for the rest of his days. Your attainment of esthetic experience expands by exercise. At times there will come a vision that is peculiarly your own. Then it should be crystallized in some form of expression—in words, lines, colors. If you have the technic, you can bring it off; if not, you will bungle it. That is why I have always guided you into drawing and painting, urged you to develop your writing and to perform on a musical instrument, and insisted that you write and talk flawlessly. No one will look at your work if you do not. The technic must be ready to hand; the taste and critical ability to know if it is good must be immanent. These can be taught, but whether you have anything to express is up to you.

Let us be grateful for the society and companionship of women! With them all stuffiness melts like cotton candy in a small boy's mouth. They know what is important and what is fun. Yet, they do their work and keep their heads fairly well. Compare a group of working women with a group of working men. The women make a party of every birthday, have showers for the prospective brides among them, have the sense to go home at five, and like to take a few moments to chat. They don't get ulcers, coronaries or gluteal callosities. They do their work faithfully and well, although without imagination; their lives are not devoured by fruitless ambition or corroded by disappointment. They will forego a position with an increase in salary which they badly need to stay where they are happy and have friends. They are content with a few

(Continued on page A-80)

herapeutic vitamins in the "therapeutic" jar

y severe disease process undermines the nutritional integrity of tissue.[1] To counteract physiologic ss depletion of B and C vitamins, prescribe high potency STRESSCAPS . . . in burns . . . fractures . . . ere infection . . . surgery . . . and in chronic disorders such as arthritis, alcoholism or colitis.

The attractive STRESSCAPS jar also plays an important therapeutic role . . . reminding the patient of daily dosage . . . assuring adequate intake for full metabolic support.

capsule contains:

amine	
ononitrate (B_1)	10 mg.
flavin (B_2)	10 mg.
inamide	100 mg.
rbic Acid (C)	300 mg.
loxine HCl (B_6)	2 mg.
min B_{12}	4 mcgm.
Acid	1.5 mg.
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ege dose 1-2 capsules daily.

STRESSCAPS®

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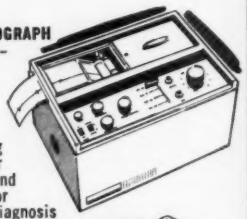
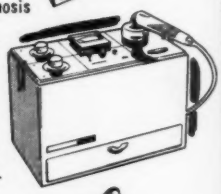
RESEARCH

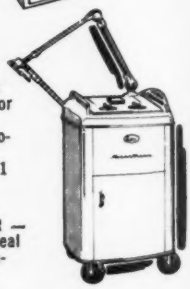
ELECTROCARDIOGRAPH —The new dual-speed EK-III has been given enthusiastic acclaim by doctors everywhere, providing either 25 mm. or 50-mm-per-second paper speed—for more accurate diagnosis under the most difficult situations.



ULTRASOUND — The new UT-400 provides the utmost in ultrasonic versatility — either continuous or pulsed ultrasound is produced.



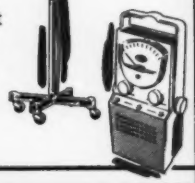
DIATHERMY — The Burdick MF-49 unit offers a compact yet effective means for every short wave application. For microwave diathermy it's Burdick popular MW-1 Microtherm.®



MUSCLE STIMULATOR — The new MS-300 is ideal for electrical stimulation of innervated muscle tissue. It provides effective therapy for the individual condition treated, **without** patient discomfort.

INFRARED — The Zoalite series has become a standard of quality and performance for the hospital physician's office and home use on prescription.

CARDIAC MONITOR — The new TC-20 Telecor monitors the heart beat during surgery, either electrically or mechanically. An invaluable instrument with many applications.



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fine things but have the capacity of enjoying more. If unmarried, they can be much more self-sufficient than a man similarly situated, who will suffer any inconveniences of ménage rather than set up cooking facilities. Although living alone, they enjoy a balanced daily life —working, cooking, sewing, decorating.

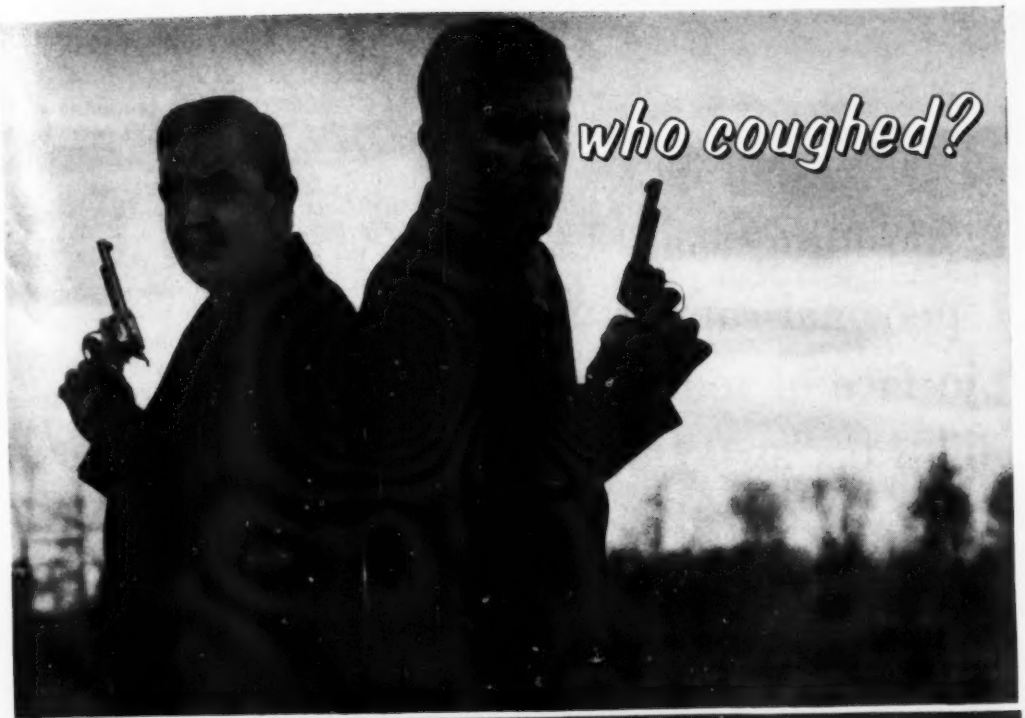
We men could learn much in integration of life from the woman who works. The time you spend with women over 25 is not wasted. With younger women conditions are different, but you know more about these things than I do, and I couldn't possibly advise you.

It would be tempting to go on and on advising you about women, talking like a wiseacre, when in reality I have to confess I still am sure of nothing regarding this subject; you will have to find out for yourself.

You will be returning home next week, so what has turned out to be a series of Chesterfield letters comes naturally and mercifully to a close. It would seem that everything of advice has been written that could be; yet, there are several fundamentals that have not been mentioned which, even by themselves, would carry you far. You remember how I used so often to say, "Do something; be something," and how you decided that was very important. Now that the fulfillment of that axiom seems imminent, I would substitute the watchword "effort." If you constantly put forth real effort at all times, you will separate yourself from the great mass of timeserving humanity, and you cannot fail to achieve in a variety of fields. I don't mean achievement only in your scientific research, but in attempting to express your thoughts in lecture or conversation, in observation and reflection as you walk down the street, in improving your stroke in swimming. The feeling of effort becomes a habit, and without it you don't feel consummate. I would supplement this with one more watchword. I thrill whenever I see it in big letters on the pavement of Lake Shore Drive: "Alert. Alert. Alert." What a word! What a motto!

But now this must come to an end. I have seemed cynical, I know, but if you ever turn to these letters again, it will be not when you are triumphant, but rather when you are in trouble. You yourself may feel cynical, and this will at least make your cynicism articulate. These are attitudes I have come to at

(Continued on page A-82)



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Hycomine SYRUP

THE *complete* Rx FOR COUGH CONTROL

cough sedative / antihistamine / expectorant

- relieves cough and associated symptoms in 15-20 minutes • effective for 5 hours or longer
- promotes expectoration • rarely constipates
- agreeably cherry-flavored

Each teaspoonful (5 cc.) of Hycomine® contains:

Hycodan®	
Dihydrocodeinone Bitartrate 5 mg.	6.5 mg.
Homatropine Methylbromide 1.5 mg.	
Pyrilamine Maleate	12.5 mg.
Phenylephrine Hydrochloride	10 mg.
Ammonium Chloride	80 mg.
Sodium Citrate	80 mg.

Supplied: As a pleasant-to-take syrup. May be habit forming. Federal law permits oral prescription.

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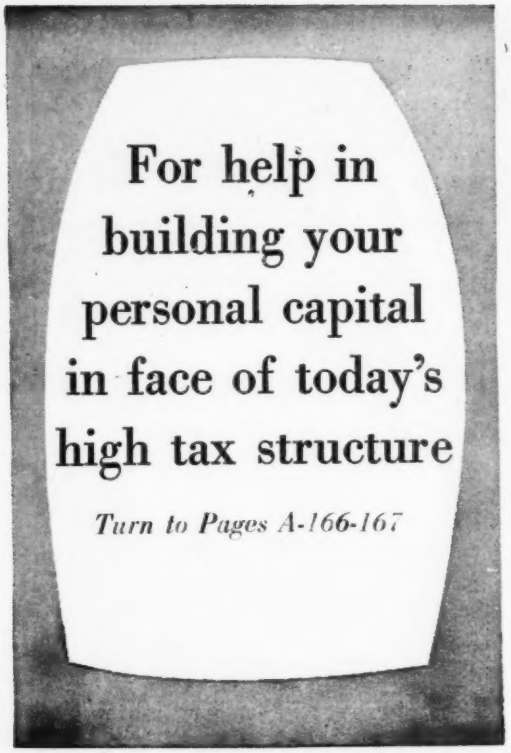
great expense; if any of them can shorten your apprenticeship in the academic life and smooth your way, I shall be glad I wrote you these letters.

Just one word more before I close, or the letters would be incomplete. Your personal religion will have to be what you integrate from your life experience and your view of the universe. If you do not find a complete answer in the legends which have grown up around one great teacher of men who lived long ago, do not let it trouble you too much. God is much bigger than the image that many devout people have made of Him. All my life, I have studied the workings of Nature, have tried to understand them and have found them miraculously complex, especially that greatest work—man. I have developed a profound respect for Nature's workings. Beyond that I cannot understand, any more than a dog can form a theory of language based on the few sounds that have meaning for him. With Disraeli one can say, "All thinking men have a religion of their own, but they never tell what it is."

And so, au revoir!
Father



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"COTHERA"® COMPOUND

BROADENS THE RANGE OF COUGH/COLD THERAPY

Effective antitussive ("Cothera")
TO MODERATE THE COUGH PROMPTLY—SPECIFICALLY
without sedation and respiratory depression

Newest antihistamine ("Theruhistin")
TO COUNTERACT HISTAMINE-INDUCED SYMPTOMS
with full potency and virtually no sedation

Systemic decongestant (*l*-phenylephrine HCl)
TO RELIEVE SINUS AND NASAL BLOCKAGE
by direct, sustained vasoconstricting effect

Analgesic-antipyretic (acetaminophen)
TO RELIEVE PAIN, FEVER, AND HEADACHE
through potent but selective central action

Expectorants (ammonium chloride, sodium citrate and chloroform)
TO SOOTHE IRRITATED MUCOSA AND PROMOTE EXPECTORATION
by demulcent, liquefying, and counterirritant properties

IN PALATABLE SYRUP FORM

Each teaspoonful (5 cc.) contains:

Dimethoxanate HCl	25 mg.
Isothipendyl HCl ("Theruhistin")	2 mg.
l-Phenylephrine HCl	5 mg.
Acetaminophen	100 mg.
Ammonium chloride	100 mg.
Sodium citrate	50 mg.
Chloroform	0.25%

Contains 10% alcohol

Usual dosage: Adults—1 to 2 teaspoonfuls (5 to 10 cc.). Children (2 to 8 years)—½ to 1 teaspoonful. Three or four times daily.

Supplied: No. 936—Bottles of 16 fluidounces and 1 gallon.

Also available

"COTHERA" SYRUP

Brand of Dimethoxanate hydrochloride

CONTROLS THE COUGH...

Selectively—preserves the useful function of the cough reflex. *Safely*—non-narcotic. No toxicity reported. *Swiftly*—acts within minutes... lasts for hours. *Surely*—preferred to dihydrocodeinone by 12 out of 15 patients.*

Usual dosage: Same as for "Cothera" Compound.

Supplied: No. 934—25 mg. per 5 cc. (tsp.), bottles of 16 fluidounces and 1 gallon.

*Klein, R.: Antibiotic Med. 5:462 (July) 1958

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Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Failure to grow in infancy—In the *Medical Journal of Australia*, Dr. Howard Williams reported that most causes of a lack of growth in infants can be determined by the basic procedures in clinical medicine, namely, a complete clinical history, observation of both mother and baby, a thorough physical examination, and the application of such simple laboratory tests as microscopic examination of the urine, bacteriologic examination of body fluids, agglutination tests, a Mantoux test, and x-ray examination of the heart and lungs. With these tests, the clinician will be able to diagnose all common disorders, such as inadequate care of the mother, poor nutrition, infections, or a gross defect of one of the vital organs. However, if a thorough clinical examination and these routine tests do not reveal the cause, special investigations must be undertaken.

Simple tests for malabsorption include microscopic examination of the stool for fat globules in cases of fibrocystic disease, with the sweating test providing confirmatory proof. Celiac disease and any other suspected steatorrhea should be confirmed by a three to five day fat-balance technic. If steatorrhea is not found to be caused by celiac or fibrocystic disease, radiologic and bacteriologic examination of the alimentary tract is necessary and it is possible that laparotomy will be required.

Abnormal patterns of serum electrolytes will often suggest disturbances of water and electrolyte metabolism, such as hypernatremia in pitressin-resistant diabetes insipidus, hyponatremia in salt-losing renal lesions and in hypoadrenocorticism, and hypokaliemia in cystine storage disease and in some renal lesions. Hyperchloremia occurs in lesions that disturb the carbonic anhydrase renal mechanism, as well as in some cases in which the ureters have been implanted in the colon. Detailed tests of renal function will be necessary in some cases in order to prove that the disease is of renal origin.

Some endocrine disorders may be difficult to investigate and diagnose; however, an infant with mild cretinism usually will exhibit slow growth, retarded epiphyseal development, an increased level of serum cholesterol, and a low content of protein-bound iodine.

Radiologic examination of the skeleton should be carried out in all instances in which the cause of slow growth is obscure. This procedure may reveal some cases of chondro-osteodystrophy, rickets and reticuloendotheliosis.

AUSTRIA

Thrombotic thrombocytopenic purpura—At a meeting of the Society of Physicians in Vienna, H. Zischinsky and O. Pendl reported a case in which the findings were characteristic of thrombotic thrombocytopenic purpura. The patient was a 15 year old

(Continued on page A-94)

In Coronary Insufficiency...

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.

Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

IMPROVED CORONARY BLOOD SUPPLY with Miltrate increases his exercise tolerance.

Miltrate*

Miltown® (*meprobamate*) + PETN

Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Supplied: Bottles of 50 tablets.

Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

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girl, probably one of the first persons in Austria to have this kind of hemorrhagic diathesis. The clinical examination revealed only an acute hemolytic anemia, of which the origin remained obscure. The true nature of the disease was detected at the postmortem examination, especially through histologic studies.

Thrombotic thrombocytopenic purpura was first recognized by Moschcowitz in 1924. It is manifested by acute onset with fever, acute acquired hemolytic anemia, a purpural rash with a low thrombocyte count, and neurologic defects. Its cause is unknown, and antigen-antibody reactions are unlikely. Since a few cases are on record in which the disease developed following some prophylactic vaccination, the possibility of an allergic pathogenesis also should be considered. The outcome is unfavorable. The disease occurs in people of different age groups; cases have been observed even in infants.

Since the etiology of this disease is not known, no reliable treatment is available. In one unique case, the patient is still alive after two years of therapy with cortisone, but whenever this course of treatment is interrupted a relapse immediately follows.

Zischinsky and Pendl showed several lantern slides of various organs, all of which revealed changes characteristic of thrombotic thrombocytopenic purpura, including edematous swelling of the intima of the precapillaries, with fibrinoid deposits and histogenetic granuloma formations, and subsequent thrombosis of the vessels. Not even microscopic examination revealed the genesis of the vascular changes.

Zischinsky and Pendl stated that the site of the primary lesion in thrombotic thrombocytopenic purpura is in the wall of the vessels, according to the interpretation of Hunziker and Oechslin of the Uehlinger Institute. However, St. Wuketich pointed out that from the slides shown it was easy to arrive at another conclusion; namely, that there is a mural intravascular thrombosis which adheres to the wall and subsequently becomes covered with endothelium, thus being apparently included in the vessel's wall. Pendl replied that from longer deliberation and scanning of the numerous different old foci of vascular lesions, he had concluded that the observed alterations were of intramural origin. He did not see a typical thrombus or find anything in the nature of a formation of a thrombus; the typical initial image always was that of a histogenetic granuloma.

St. Wuketich also commented on the term "fibrinoid," which Pendl used to describe the deposits in the vessels. This word usually designates a substance which resembles fibrin; however, Gitlin and Craig of Boston histochemically proved that the fibrinoid actually is fibrin. They also proved that from the tinctorial aspect the fibrin will only behave orthochemically when it contains at least 1 gm. per cent of albumin. In other words, the failure of a certain staining of fibrin is still no proof for the assumption of a "fibrinoid" deposit. Pendl answered that the term "fibrinoid" does not mean any definite substance; it is used merely to label a protein stuff in the sense used in the article of Craig and Gitlin.

E. Keibl mentioned that a patient with a similar case of thrombotic thrombocytopenic purpura was under treatment and observation at the Novotny Clinic. He pointed out that hemolytic anemia and defects in the central nervous system are not the only cardinal symptoms of the disease. The number of thrombocytes is greatly reduced, and damage to the renal vessels appears to be essentially the same vascular lesion as was shown on the lantern slides of the first case discussed. This renal lesion results in proteinuria, in the appearance of red blood cells and casts in the urine, and in renal failure.

The patient whom Keibl described reacted to treatment in a remarkable manner. The disease had a fulminant onset. The patient was transported to the clinic in a comatose condition with a hemolytic crisis. She was given blood transfusions and large doses of cortisone, but remained unconscious. Only when intravenous injections of chlorothiazide resulted in marked dehydration did the patient become more lucid, and the following day she was able to carry on a conversation. Possibly, an edematous swelling was also a contributing factor in the origin of the defects of the central nervous system which were provoked by vascular lesions and possible hemorrhages. Therefore, the acute condition was overcome in this patient, and even the hemolytic anemia was brought under control. However, renal insufficiency, with residual nitrogen values up to 100 mg. per cent, developed in this patient, and it is questionable whether or not this condition will ever abate.

Zischinsky closed the discussion with the remark that the nervous symptoms in thrombotic thrombocytopenic purpura are not the result of

(Continued on page A-96)

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brand of phenylbutazone

in arthritis and allied disorders

proved by a decade of experience

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Repeatedly it has been demonstrated that Butazolidin:
Within 24 to 72 hours produces striking relief of pain.
Within 5 to 10 days affords a marked improvement in mobility and a significant subsidence of inflammation with reduction of swelling and absorption of effusion.

Even when administered over months or years Butazolidin does not provoke tolerance nor produce signs of hormonal imbalance.

Butazolidin® (brand of phenylbutazone): Red-coated tablets of 100 mg.
Butazolidin® Alka: Capsules containing Butazolidin® 100 mg.; dried aluminum hydroxide gel 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide 1.25 mg.

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hemorrhage in the brain, but are caused by vascular changes which are similar to those seen in the other organs.

BRAZIL

Hirsutism—J. Rodrigues and co-workers at the Moncorvo Filho Hospital in Rio de Janeiro made clinical and hormonal investigations of 19 cases of varied degrees of hirsutism. Operations were performed on six patients; in addition to bilateral ovary wedge resection, a bilateral biopsy of the adrenals was done.

In each case, tests performed included determination of total 17-ketosteroids, dehydroisoandrosterone, pregnanediol, 17-hydroxycorticoids, 11-oxysteroids, estrogens, and the glucose-insulin tolerance curve. In addition, chromatographic fractionation of 17-ketosteroids was done.

The investigators reached the following conclusions: (1) At present, no isolated test is capable of determining the cause of hirsutism. (2) From the results of histopathologic examinations and the administration of hormones, it seems probable that the Stein-Leventhal syndrome is caused by an adrenal hyperfunction of androgenic origin. (3) The glucose-insulin curve was abnormal only in cases of marked metabolic hyperfunction of the adrenals. (4) The most common chromatographic alteration was the increase of fractions II, III, VI and VII.

This report was published in *Arquivos brasileiros de endocrinologia e metabolismo.*

Genital schistosomiasis in women—In *Revista de gynecologia e d'obstetricia,* A. Camara advocated the consideration of schistosomiasis as a gynecologic factor because of its frequency and significance. He reviewed the published Brazilian cases and explained that the small number of such cases is due to the lack of systematic histopathologic examination. Dr. Camara emphasized that genital schistosomiasis has no symptomatology of its own in spite of the fact that some foreign investigators have stated that it does have a specific symptomatology. He described three cases from his own records, all of which were successfully treated.

Endometriosis—C. A. Salvatore and J. Galluci reviewed 134 cases of endometriosis found at 1,250 gynecologic operations (980 laparotomies and 270 vaginal hysterectomies) performed at the gynecologic clinic of the Faculdade de Medicina da Universidade de São Paulo. In *Anais brasileiros de ginecologia,* they reported the following observations.

1. Endometriosis was present in 10.7 per cent of the cases. The condition was external in 0.96 per cent and internal in 9.75 per cent.

2. Internal endometriosis was found in 51 per cent of patients between the ages of 40 and 50, and external endometriosis was found in 75 per cent of patients between the ages of 30 and 50.

3. Symptoms included dysmenorrhea, hypogastric pain, metrorrhagia and hypomenorrhea. However, in most cases, the symptoms resulted from associated lesions and therefore could not be considered characteristic of endometriosis.

4. In 46 cases of endometriosis not associated with other lesions, metrorrhagia was present in 21.7 per cent and dysmenorrhea in 19.7 per cent.

5. The incidence of sterility was found to be high in pelvic ovarian endometriosis and low in internal endometriosis.

6. Forty-nine of the 134 patients (36.5 per cent) also had a uterine myoma; 16 (11.1 per cent) had carcinoma of the uterine cervix, and 17 (12.6 per cent) had prolapse of the uterus.

7. Most of the cases of external endometriosis and almost all the cases of internal endometriosis were diagnosed as myoma and functional hemorrhage. Diagnosis is usually established by histologic examination of the specimen.

8. Surgical treatment seemed to be adequate in the majority of cases.

ENGLAND

Preoperative medication in children—The current trend of preference in the choice of preoperative medication for children appears to be shifting from basal narcosis to preoperative sedation. This may be due to the growing appreciation of the need to assure rapid recovery from the anesthetic and to avoid nightmare delirium during the immediate postoperative period. All authorities are agreed on

(Continued on page A-98)

in oral penicillin therapy

the speed of action you want

the reliability you need

Penicillin, still the most frequently prescribed antibiotic, assumes new reliability in the form of PEN·VEE K. Tablet or Liquid PEN·VEE K may be prescribed for all infections responsive to oral penicillin . . . *including many usually treated with parenteral penicillin.*

The speed of action and reliability of oral potassium penicillin V have been dramatically demonstrated by recent studies[1,2] in which 107 subjects were each given 400,000 units of the antibiotic. Appreciable penicillin levels were consistently produced within 15 minutes; peak levels within one-half hour. Penicillin levels still persisted in all subjects at two hours, and in 93 per cent of subjects at four hours.

1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. *5*:139 (Feb.) 1958.

PEN·VEE® K

Liquid: Penicillin V Potassium for Oral Solution;
Tablets: Penicillin V Potassium, Wyeth

Wyeth
Philadelphia 1, Pa.

SUPPLIED: *Liquid*: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Both supplied as vials of powder to make 40 cc. *Tablets*: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

the importance of a child's upbringing, the value of a sensible attitude of the parents toward the prospect of his admission to the hospital, and the innate tendency on the part of the child himself to cooperate. Also important is a sympathetic attitude on the part of the hospital staff.

Dr. Andrew G. Doughty, consultant anesthetist to the Richmond and Kingston Hospitals, read a paper recently at the Royal Society of Medicine on the evaluation of premedication in 318 children, most of whom underwent adenotonsillectomy. They were intubated and maintained at a light level of anesthesia with nitrous oxide, oxygen and a trace of halothane, trichloroethylene, or ether. They were all given one of three methods of premedication: (1) atropine only, by injection; (2) papaveretum (OMNOPON®) and hyoscine, by injection; and (3) methylpentynol (OBLIVON®) and hyoscine, by mouth.

According to the criteria defined in the study, methylpentynol-hyoscine appeared to be a satisfactory premedication, whereas papaveretum-hyoscine showed little advantage over atropine alone. Nevertheless, if different criteria were adopted papaveretum-hyoscine could also be shown to be highly satisfactory. Studies showed that only in the unsedated children were advancing years associated with a marked improvement in behavior

In attempting to reconcile these opposing views, one can formulate what may be called "the ideal premedication," which, if obtainable, would be acceptable to all. The qualifications are: (1) The child should accept the prospect of venipuncture with equanimity, and should not move or cry at the time of the injection; (2) the premedication should not be associated with respiratory depression; (3) the premedication should not be associated with postoperative vomiting, crying or restlessness; (4) the child should retain no unpleasant memory of the intravenous induction.

If these ideals are applied to the three methods of premedication, the following numbers of children behaved satisfactorily before, during and after the operation: with atropine only, 2 of 93 (2.2 per cent); with papaveretum-hyoscine, 9 of 91 (9.9 per cent); with methylpentynol-hyoscine, 8 of 91 (8.8 per cent). These figures seem to emphasize that the field is wide open for the introduction of a really satisfactory premedication for children. Meprobamate (EQUANIL®), mepazine (PACATAL®), and trimeprazine (VALLERGAN®) are said to be promising.

Oral treatment of diabetes—In an article in the 1959 fall number of the *Practitioner* entitled "Advances in treatment," Dr. Wilfrid Oakley of King's College Hospital, London, stated that the most important advance in the treatment of diabetes in recent years has been the introduction of the oral hypoglycemic agents. In 1942, while investigating the chemotherapeutic action of the sulfonamide preparation IPTD, Professor Jambon and his colleagues at Montpellier observed that it caused hypoglycemia, and in 1955 Franke and Fuchs in Germany recognized the hypoglycemic action of the related compound carbutamide. Since its discovery several new hypoglycemic sulfonamide derivatives have been produced, of which the two most important are tolbutamide and chlorpropamide.

The great majority of severe diabetics, and the majority of moderately severe diabetics fail to respond to oral agents, says Dr. Oakley. This means that it is not only a waste of time, but may be dangerous, to use them in the treatment of any diabetic who, without insulin, is liable to develop significant ketosis. The type of diabetic who may be expected to respond well is the relatively mild, usually middle-aged or old, often obese and aketotic patient, whose disease can be controlled either by strict diet alone or with the addition of a small dose of insulin. Not all so-called suitable cases respond to the preparations at present available, the reason for failure being unknown. As with insulin, obesity should generally be regarded as a contraindication to the use of oral preparations; the correct treatment is weight reduction by means of a restricted-carbohydrate low-calorie diet. The use of oral agents should therefore be restricted to those mild or relatively mild diabetics in whom (1) diet alone fails to bring the blood sugar within or near to the normal range; (2) the dietary restriction required to control the diabetes causes progressive loss of weight or severe hunger; (3) the withdrawal of insulin is not followed by relapse into significant ketosis; (4) the dose of insulin that can be replaced is usually not more than about 30 units.

In addition to these general indications there may be some special reason for wishing to take a patient off insulin, such as blindness or the danger of nocturnal hypoglycemia in elderly patients living alone. The mild diabetes which is sometimes produced by prolonged steroid therapy can be controlled by oral agents.

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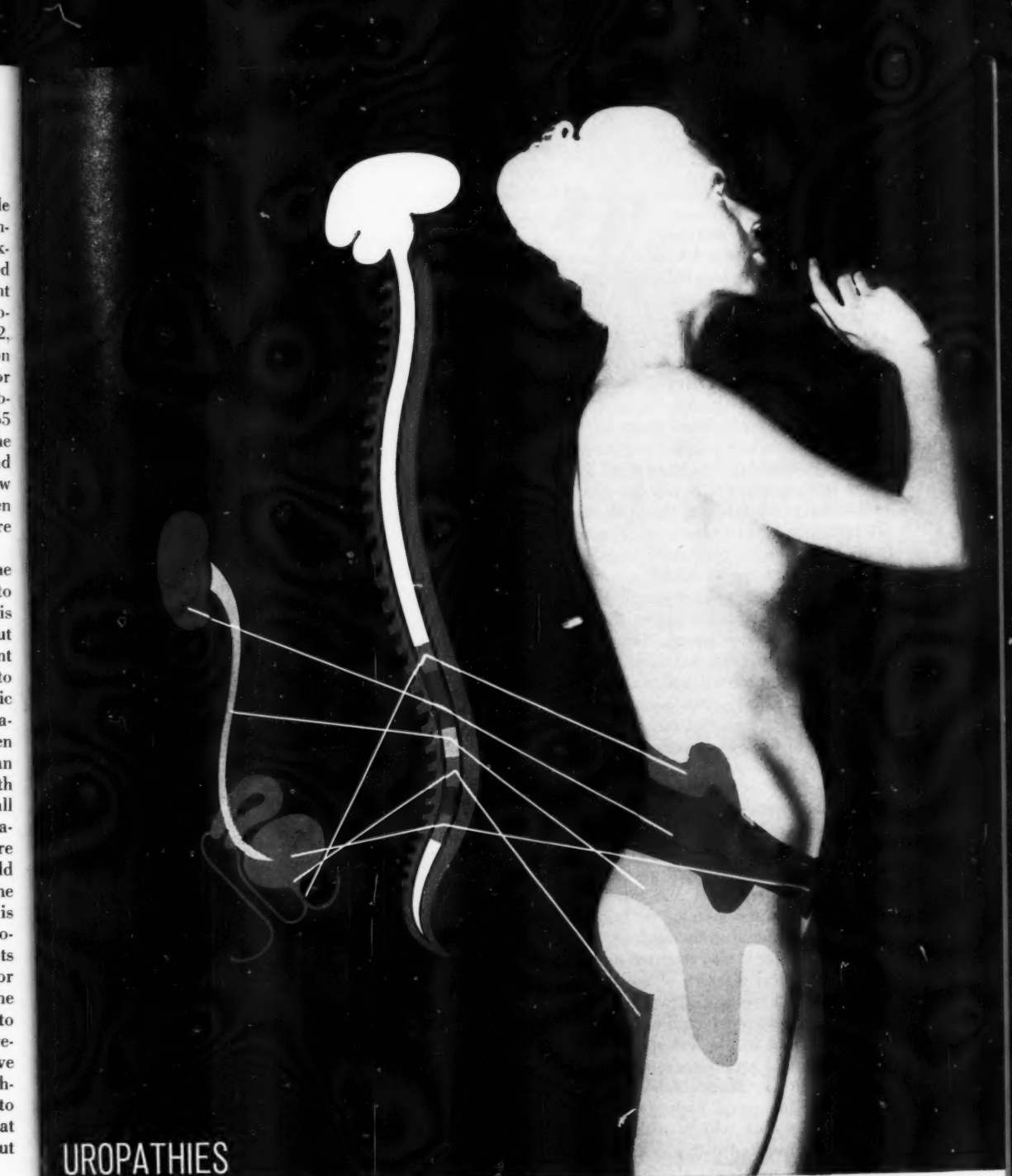

UROPATHIES

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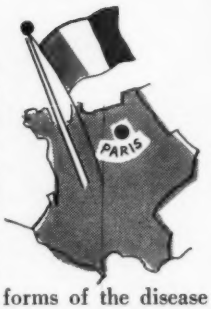


Hodgkin's disease—The opinions expressed by several Parisian hospital physicians during a conference on Hodgkin's disease have been published in *La semaine des hôpitaux de Paris*. Professor Bariéty pointed out that the so-called isolated mediastinal forms of the disease are never pure forms. They are always accompanied by extensive involvement of the bronchi, lungs and pleura, which can be seen either by radiography, after filling the mediastinum with air (gas), or by bronchoscopy. Diagnosis is difficult, since the only signs of the disease, such as cough, shortness of breath on exertion, and chest pain, may remain atypical. Forms of the disease with alterations above the pulmonary hilus are slow in developing. Radiotherapy is of little help. Some cases have been mistaken for malignant tumor or for tuberculosis, their true nature having been revealed only by a pneumonectomy. However, this surgical treatment has never been of any value in Hodgkin's disease.

Professor Delarue discussed the pathologic anatomy of the primary pulmonary Hodgkin's granulomas. Actually, these granulomas are composed of isolated nodules. Between the nodules, the parenchymatous masses are not ventilated; they are invaded by a "lipid pneumonia" which is reticular, hypertrophic and utterly steadfast. Only the Hodgkin's nodules contain the Reed-Sternberg cells found in the sputum.

Professor Delarue also reported on the histology of the atypical diseases of the lymph nodes. Many atypical histologic pictures are deceiving. These include sclerotic lymph nodes which either are far advanced in the disease or are modified by radiotherapy; lymph nodes with suppurating inflammation or necrosis which no longer resemble the Hodgkin's lymph nodes; and a Hodgkin's reticuloendotheliosis which, with its vague inflammatory forms and with an absence of granulomas, remains unrecognizable and assumes the aspect of Schaumann's disease. In addition, by an unfortunate turn of events, a biopsy may pick out a lymph node which has remained healthy. Yet, as Dr. André asserted, a needle biopsy of the lymph nodes, which can be repeated as desired, will reveal the pathognomonic Reed-Sternberg cells in 80 per cent of the cases. This is often the only way to distinguish Hodgkin's disease from the reticulum-cell sarcomas and the spinous-cell carcinomas of the lymph nodes.

Among the symptoms which suggest the diagnosis of Hodgkin's disease is the occurrence of pain on the consumption of alcohol. This was the earliest symptom in a third of the cases studied. Centered in the skeleton or in a group of lymph nodes, the pain occurs a few minutes after the patient drinks a glass of wine or liquor; it disappears spontaneously in a few hours.

The prognosis of Hodgkin's disease was studied by Professors Marchal and Croizat and by Madame Lamotte Barillon. The duration of the disease varies between three months and 13 years from the time of the diagnosis. The average duration is four years, but half of the patients studied died before two years of illness had elapsed; one-fourth of them died after six years of illness. Although age is apparently not a factor, the majority of the long survivals are in patients in the 30 to 40 year old group.

The coexistence of tuberculosis with Hodgkin's disease has been particularly observed in the form in which acute attacks of granulosis or pneumonia occur after treatment with corticosteroids. Types of the disease which may prove fatal within a period of two years are the acute anemic galloping forms, the mediastinal hilar forms that cause difficulty in breathing, the spinal forms with paraplegia, and the digestive forms with occlusion or intestinal perforations.

The portion of the discussion concerning treatment did not elicit any original observations. Professor Jean Bernard reported that he favors surgical removal of a recently formed, isolated, large lymph node whose puncture confirms the diagnosis.

Aphthae of the mouth—In *La Presse médicale*, Dr. R. Lacassie has published a report on 38 patients who had aphthae of the mouth. He gave these patients daily subcutaneous injections of 250 mg. pyridoxine (vitamin B_6). No more than five injections were needed. The pain was immediately stopped and prompt cure resulted in all but three cases. Normal diets were resumed the day following the disappearance of pain. The inflammation receded but the scarring of the small central yellow ulceration, which is characteristic of aphthae, required several days.

If fever is present, it drops in 24 to 48 hours with the described treatment. The same results are achieved in recurrent attacks of aphthae of

(Continued on page A-103)

the mouth. The treatment has no untoward effects. It is particularly interesting to know that pyridoxine is effective in treating a disease which does not respond to local measures. The mode of action of pyridoxine remains unknown.

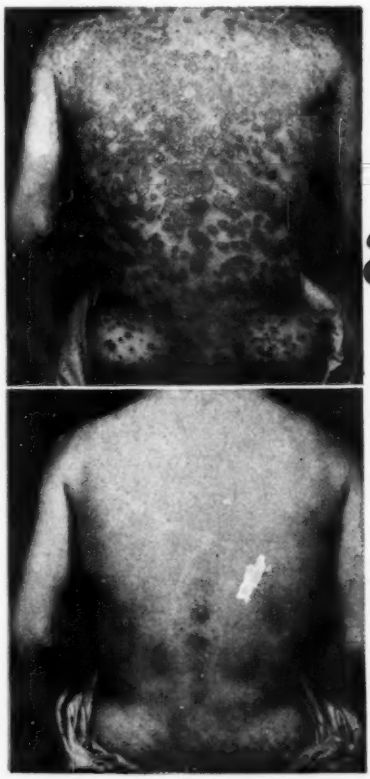
GREECE

Abnormalities of hemoglobin—In the *Evangelismos Hospital Review*, Professor A. Gouttas, head of the Clinic of Internal Medicine, University of Athens Medical School, and his associates I. Tsevrenis and A. Papaspyrou reported on the frequency with which various abnormalities of hemoglobin occur. In a study of 345 patients, they found 13 cases of sickle-cell anemia, 36 of Cooley's anemia with type S hemoglobin, 40 of thalassemia major, 28 of sickle-cell trait, 217 of thalassemia minor, and 11 of Cooley's anemia with type H hemoglobin. Results of this study seem to indicate that Cooley's anemia is the most prevalent type of hemoglobin abnormality seen in Greece. However, no statistical data support this observation.

Since examination of a large number of people is necessary in order to obtain accurate data and percentages, Professor Gouttas and co-workers, sponsored by the Royal Research Institute, have begun a study of the inhabitants of Euboea Island, an area in which many cases of hemolytic disorders already have been found.

Professor Gouttas also reported that type E hemoglobin has been found for the first time in Greece in two sisters of pure Greek ancestry. The girls were first examined in childhood before electrophoresis was available; at that time, Mediterranean anemia was diagnosed. Recently, however, they were hospitalized with severe hemolytic crises, and electrophoretic analysis of their blood revealed the presence of types E, F and A hemoglobin. Their father was found to have the E trait, and their mother had the characteristics of thalassemia minor.

Electrophoretic analysis has become available only recently, and Professor Gouttas suggests that perhaps more cases of Cooley's anemia with type E hemoglobin would be found if anemic patients were re-examined with the newer method.



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*Combes, F. C.: New York State Jrl. Med., 54:13 Pg. 1945, (July) 1954.
*Fox, C. F.: The Treatment of Common Skin Diseases, G.P., 20:1 (July) 1959.
**Rosenthal, T.: Management of Psoriasis, In Press.

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SPECIAL ISSUE

University of Michigan Medical School

WINTHROP N. DAVEY, M.D.
Guest Editor

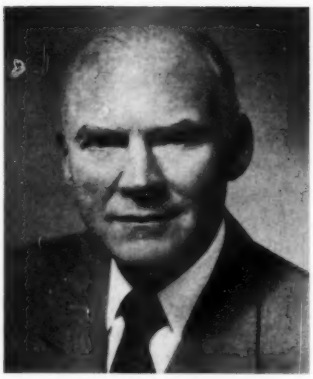
JANUARY 1960

Postgraduate Medicine

INTRODUCTION

At a time in history when medicine is moving forward at a tremendous pace, when experiments to improve medical education are the aims and ambition of medical educators, when the aspirations of many of our great sciences are turned to the conquest of disease, our future hopes at the University of Michigan are inspired by the completion and availability of the first unit of the new Medical Science Building. This modern facility, so carefully planned and constructed for medical education and research, was promptly put to usage for continuing advances in many areas of pharmacology, biochemistry and administration. It provides facilities that encourage creativity and furnish an inspiration for the development of new ideas and technics among our scientists in their respective fields. Its influence in promoting a better correlation between the basic sciences and clinical medicine is strongly felt in that it is an integral part of our Medical Center in close association with clinical medicine.

A policy that needs constant attention and further exploration each year is that of medical student admissions. We must choose students with adequate intellectual attainments and proper motivation for the study of medicine. In our search for well-qualified medical students, nearly every college in Michigan is visited by members of the Admissions Committee. Conferences are held with members of the faculty of these institutions in an effort to familiarize them with our admissions policies and the qualifications we are seeking in candidates for the medical profession. Without exception our hosts are keenly interested in our



DR. FURSTENBERG

evaluation of the potential doctor and are eager for contacts with our faculty and for an exchange of viewpoints with them. On many occasions applicants are interviewed at their respective colleges.

In keeping with our pledge to the state of Michigan and to the nation in 1951 to do everything in our power to increase our medical man power, we again accepted 200 freshman students when the Medical School commenced its one hundred-eighth year on September 22, 1958. This was the eighth consecutive year that this program had been put into effect. A visitor to our Medical Center cannot fail to be struck by the size of our undergraduate and graduate bodies, the modern facilities for medical education and research, and the care given our patients in the new Outpatient Building, the 1000 bed University Hospital and the affiliated 500 bed Veterans Administration Hospital.

The medical faculty is aware of the challenges that face American medicine today and is dedicated to the responsibility of doing its part to meet them. Among these challenges the need for increased medical man power is the common denominator of them all. Without it efforts to solve the problems of mental health, chronic illness, rehabilitation and preventive medicine are futile. The faculty can be proud of the action it took eight years ago to increase its undergraduate student body to one of the largest in the nation. It is still convinced that we must continue to be pre-eminent in producing doctors for education, research and the care of the sick.

A. C. FURSTENBERG, M.D.*

*Dr. Furstenberg retired as Dean of the University of Michigan Medical School in June 1959.

Serious Reactions to Penicillin

DONALD C. NILSSON* AND JAMES C. SISSON†

University of Michigan Medical School, Ann Arbor

Hidden sources of exposure to penicillin may assume great importance as the use of this antibiotic continues to increase. Possible sources include milk and dairy products, mold in household articles and food, contaminated syringes, vaccines containing penicillin, and penicillin dust in the air.

Statistical evidence indicates that only a few absolute indications for the use of penicillin remain.

If a patient's history strongly suggests sensitivity to penicillin and the physician is unable to devote the time to perform the procedures necessary to protect the patient's safety, it may be wise to refer him to someone who makes these tests routinely.

Measures for treating anaphylactoid and other reactions to penicillin are outlined.

FOLLOWING its introduction to the medical profession, penicillin was warmly received because of the frequent reactions to sulfonamides and because of their limited therapeutic spectrum. Penicillin appeared to be virtually nontoxic and of low antigenicity.

DONALD C. NILSSON

Soon afterward, however, Keefer and associates[1] reported the development of fever, urticaria, chills, headache and myalgia in seven of 500 patients treated with penicillin. Pillsbury and coauthors[2] then called attention to the rising incidence of urticaria after a second course of the drug; after the first course the incidence in a large series was 1.8 per cent, and after the second course it was 6 per cent. These reports were ominous warnings of events to transpire in later years. The literature contains hundreds of reports of reactions to penicillin, leaving little doubt of the drug's allergic potential. Maganzini[3] in 1957 stated that penicillin was the most frequent source of "drug reaction," having long since supplanted horse serum, aspirin, quinine and ipecac.

We feel justified in re-emphasizing the seriousness of this problem, particularly the fatal anaphylactoid type of reaction to penicillin. Further, attention should be focused on predicting such an event and on managing other serious reactions when they occur.

Serious or life-threatening reactions to penicillin may be defined as (1) anaphylactoid reaction (most common); (2) superinfection of serious degree; (3) serious skin reactions, in particular, exfoliative dermatitis; (4) angioneurotic edema with involvement of the respiratory tract, and (5) blood dyscrasia. A sixth condition, polyarteritis nodosa, should

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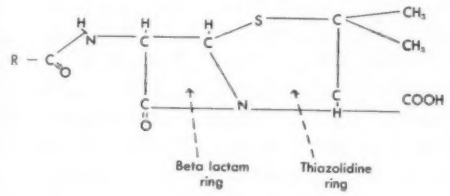
be included in this list, although it is often difficult to incriminate penicillin as an etiologic agent.

Von Oettingen[4] listed 14 types of complications of antibiotic therapy. Other authors[5] have listed as many as 50. All these reactions deserve consideration, but we will confine our remarks here to the most serious ones.

Historical Data

Penicillin is derived as a metabolic product of many species of *Penicillium* mold, *P. notatum* being the most common source.[6] Its structure has been defined clearly. The most important part is the beta lactam ring.



While penicillin itself has been found to be a highly antigenic substance, the frequency and intensity of reactions increase, as one would expect, when oil, wax and procaine are used to delay absorption. A somewhat different situation exists in regard to penethamate hydroiodide (NEO-PENIL®). This product produced unusually frequent reactions,[7] some of which probably were allergic in origin but most of which were produced by true cytotoxic injury. We may speculate that the latter effect was due to partial tissue injury, insufficient to cause death of the cells but sufficient to activate the release of large amounts of histamine, serotonin or other mediators.

It would seem that the majority of reactions to penicillin are produced by the penicillin molecule itself, but in the early days of manufacture of penicillin they frequently could be ascribed to impurities in the mixtures. When substances were added to penicillin to delay absorption, many reactions were due to these substances.[8] The unique substance Neo-Penil may have produced allergic reactions, but it is more likely that most of the reactions to this compound were of a true tissue-injury type.[7]

Sources of Penicillin Exposure

As is the case with other potentially allergenic substances, it seems likely that the rate of reaction to penicillin is in some way directly related to the degree of exposure. During the first year of penicillin production in this country a total of 29 lb. was available. In 1956, 440 tons were produced. According to Welch and associates,[9] this amount would be sufficient to administer 1,470,000,000 doses of 300,000 units each. A portion of this massive quantity has been applied to nearly every structure of the human organism by every route. It is not surprising, therefore, that anaphylactoid reactions have been reported from the use of penicillin by injection, inhalation and instillation, and in tablets, troches, capsules, oral suspensions, ointments, nose drops, skin tests and vaccines.[10]

The more obvious sources of penicillin exposure are very important, but hidden sources are infrequently considered and may also be of great importance as the use of this antibiotic continues to increase.[11]

Hidden sources of exposure—1. Transfer of sensitization in utero—Penicillin traverses the placental barrier in a fetal-maternal circulation ratio of approximately 2/3:1. This may explain allergic reactions in infants after a first dose of penicillin.

2. A common antigenic effect due to the presence of human mycoses, such as those produced by *Trichophyton*—Cormia and Lewis,[12] on the basis of human and animal experiments, first suggested the possibility of common antigens between these groups of substances. The suggestion was reinforced by Peck and Hewitt[13] and by Uri and co-workers,[14] but it has not been universally accepted. The vesicular eruptions produced after penicillin injections in sites of long-dormant tinea infections have been appreciated for many years.

3. Inhalation or ingestion of spores from mold in household articles and food, closely related to the molds from which penicillin is manufactured—The possibility of the production of penicillin hypersensitivity in this manner would be suggested from the derivation of penicillin as a metabolic product of *Penicil-*

lium. Kern and Wimberley[15] were impressed with the frequency with which penicillin-sensitive persons demonstrated positive skin test reactions to *P. roqueforti*. Other workers[5] have found no relationship between penicillin and *Penicillium* sensitivities.

4. Presence of penicillin-related molds infecting such structures as pulmonary tissue or intestinal tract—While this is possible theoretically, we do not know of any substantial evidence to incriminate this method of penicillin sensitization.

5. Presence of penicillin in milk and dairy products, as suggested by Zimmerman[16]—Welch[17] reported on three surveys conducted by the Food and Drug Administration to determine the antibiotic content of milk and dairy products. From 3.2 to 11.6 per cent of the milk samples tested contained penicillin; the highest quantity reported was 550 units per quart. In the first survey at least, no antibiotic activity was found in evaporated milk, cheese, butter or dried milk. The penicillin in the milk originated from its use in the treatment of mastitis and the marketing of the milk less than three days after the last injection of penicillin into the udder of the animal. In some instances, use of the drug to reduce bacterial counts in the milk could not be excluded. The opinion was expressed that animal feeds with high penicillin content would be a rare public health problem and that the use of antibiotics for the immersion of animal products during processing or for the treatment of vegetables and fruits would not be a problem. Cases such as those reported by Epstein[18] in which a prolonged reaction to penicillin followed a single injection of penicillin not of the benzathine type probably are due to repeated reexposure to the drug in dairy products. Zimmerman[19] reported two such cases.

6. Contamination of syringes—Surely this is one of the most frequent hidden sources of penicillin exposure and one of great clinical importance. Either syringes or the water used in sterilizing solutions may account for this contamination. Coleman and Siegel[20] called attention to this problem and emphasized that this transfer could be eliminated only after separation of the syringe parts, two or more washings, and autoclaving. A solution of penicillin boiled for more than 16 hours still produced a positive passive transfer test reaction on a site previously sensitized. Coleman and Siegel rightfully condemned the method of adding new sterilizing water as the old solution boils away. A much more preferable solution would be a complete and frequent change of sterilizer water. Bierlein[21] expressed doubt that the new high-pressure sterilization used for the prevention of hepatitis is sufficient to inactivate penicillin.

7. Penicillin-containing vaccines—Recent mass immunization programs against poliomyelitis have presented exposure to penicillin to millions of persons. Fortunately, serious reactions as a result of these programs have been rare, but the quantity of penicillin in each dose of vaccine is many times greater than that required to produce anaphylaxis in an extremely sensitive person.[22] Zimmerman[10] stated that while 1 to 200 units per milliliter are permitted in the manufacturing requirements for poliomyelitis vaccine, his communications with the manufacturers would indicate a range of only 3 to 20 units per milliliter. The vaccine produced by one manufacturer contains probably no more than 0.000001 unit per milliliter. Despite these small quantities, Zimmerman reported six instances of mild delayed penicillin reactions to the vaccine which were proved to his satisfaction by penicillinase inactivation and, in some cases, by absence of reactivation when penicillin-free vaccine was given later.

8. Penicillin dust in the atmosphere—Recent experimental evidence would indicate that penicillin contamination of the air in hospitals and in plants which manufacture or distribute penicillin offers an excellent method for sensitization to this antibiotic. Destruction of this dust occurs very slowly and over a long period. Contamination in hospitals may occur from puncturing penicillin vials, washing syringes, clearing air from syringes containing penicillin, topical application of the antibiotic, and from the urine of patients. It seems very likely that this penicillin "fallout," particularly in hospitals, accounts at least in part for the marked rise in penicillin sensitivity among hospital personnel. Evidence also is strong

that it accounts for the rapid rise of penicillin-resistant staphylococci after hospitalization.

Frequency of Penicillin Reactions

The frequency of death following penicillin-induced anaphylaxis may be indicated by projecting available data in terms of the entire country. By far the most extensive investigation of this nature is that conducted by Welch and associates.[9] Their figures indicate a steady rise in serious and fatal reactions from 1953 through 1956. Approximately one-third of the hospital beds in the United States were included in a survey covering a period of nearly four years. The number of penicillin reactions recorded was 2,517, of which 901 were life-threatening. Of the latter, 809 were anaphylactoid in nature. Penicillin was involved in more than 80 per cent of all serious reactions to antibiotics, and a total of 72 deaths were recorded. By projecting these figures and those from other sources, deaths from penicillin in this country may be predicted as follows.

Welch et al.[9]	54 per year
Welch et al.[7]	86 per year
Rosenthal[23]	125 per year
Feinberg and Feinberg[22]	124 per year

One should bear in mind the rapid increase in the incidence of these reactions. Every conceivable route of administration and every form of penicillin have been incriminated. In 1955 Brown[24] stated that following injection of penicillin some reaction could be anticipated in 2.5 per cent of children, 5 per cent of nonallergic adults, and 15 per cent of allergic persons. While this incidence of reactions in children is nearly in agreement with the figures of Berkowitz and associates,[25] it is considerably higher than those reported by other workers.[5,26]

Indications for the Use of Penicillin

Despite the fact that the use of penicillin undoubtedly has saved thousands of lives, it is becoming increasingly apparent that the indications for its use deserve careful scrutiny. Reimann[27] cautioned against the indiscriminate use of antibiotics for such trivial conditions as common colds, 95 per cent of which are due to viral infections not affected by antibiotics. Grieble and co-workers[28] concluded from an extensive study of acute respiratory infections over a period of two years that in unselected cases of upper respiratory disease 5.7 per cent are streptococcal, 13 per cent are caused by known viruses, and 81.3 per cent are of unknown viral origin.

In regard to the possibility of reducing secondary bacterial infection following nonbacterial influenzalike symptoms, Jones, Bigham and Manning[29] in a series of 150 cases could find no evidence to justify such prophylaxis. Further, antibiotics did not influence the course of the illness. Bell, Ramie and Wynne[30] specifically cautioned against the use of antibiotics to prevent postsurgical infection, which occurs extremely infrequently, especially if all aseptic precautions are observed.

It would appear, therefore, that the main indication for the use of penicillin remains infection by hemolytic streptococci sensitive to the drug. Breese and Disney[31] stated that an accurate diagnosis of streptococcal pharyngeal infection could be made in 75 per cent of the cases in children and that throat cultures materially improved the diagnostic accuracy. Assuming the indication for the use of penicillin in streptococcal respiratory infections, the chance that rheumatic fever may follow such an infection without the use of penicillin is about 1.4 per cent in nonrheumatic persons.[32] The possibility of preventing this complication by the prompt and adequate administration of penicillin to patients with the general syndrome of fever and sore throat would be about 0.42 per cent. These figures would have to be revised upward slightly if one were to include glomerulonephritis and otitis media. The chance of incurring some penicillin reaction would be 2.5 per cent in children, 5 per cent in nonallergic adults, and 15 per cent in allergic persons.[24] Therefore, it would appear that the chances of harm outweigh the advantages unless the indications are extremely well defined. Subacute bacterial endocarditis produced by penicillin-susceptible organisms would seem to be one of the few remaining absolute indications for penicillin, and this only when there has been no known serious reaction to the drug.

Use of penicillin-containing poliomyelitis vaccine hardly seems justified when a penicillin-free vaccine is available. Adenovirus vaccine recently has been given a great deal of publicity in the lay press. There is little doubt that these viruses produce a great deal of morbidity among the armed forces, but in the civilian population they account for only about 1 to 3 per cent of upper respiratory illness.[28,33] Should the physician still believe that use of the vaccine is indicated, penicillin-free adenovirus vaccine is available and in our opinion is preferable to those containing penicillin.

Application of penicillin to any mucous membrane carries with it the risk of high sensitizing potential,[34-37] except for capsules or tablets, which seem to have a much lower potential than does penicillin administered parenterally.[3,9] There is little evidence to support the use of penicillin in the form of lozenges, and there is even less justification for its use in the form of eye, nose, vaginal and skin preparations; other agents probably will be as effective without the high sensitization index.

Prevention of Penicillin Reactions

The past medical history must be scrutinized carefully.

Personal history of major allergic disease—Reactions occur 3 to 10 times more frequently in allergic persons than in nonallergic ones,[5,24] and 30 per cent of anaphylactoid reactions have occurred in allergic persons.[17] Since 15 per cent of the general population are allergically constituted, one of seven patients is an excellent candidate for penicillin sensitivity.

Previous reaction to an antibiotic—The physician must question the patient carefully for any evidence of a delayed reaction occurring 7 to 14 days after administration of an antibiotic; such events are forgotten easily. Rosenthal's[23] follow-up study of 30 anaphylactoid reactions revealed that an inquiry regarding previous reactions apparently had not been made in 14 of the cases. Seven of the 14 patients had had penicillin reactions previously, and an additional three had a history of asthma. In Rosenthal's opinion, reasonable indications for use of the antibiotic were present in only 12 of the 30 cases.

History of previous administration of penicillin—Peck and associates[38] noted an incidence of penicillin reactions of 5.4 per cent among patients without known previous therapy with the drug, whereas the incidence was 25.4 per cent among those who had had at least one previous course. Brown[24] stated that there is one chance in six that some degree of reaction to penicillin will occur after a second course of therapy. Feinberg,[35] however, noted that a considerable number of persons may receive penicillin without adverse effects after having experienced a serious reaction to it previously. It is impossible to predict this loss of sensitivity, and it would seem wiser never to take the risk.[39] Spontaneous loss of sensitivity may account for some reports of tolerance to penicillin when a different type of the antibiotic is substituted for the one which induced a reaction. It is unlikely that there is a difference in antigenicity among the various types of penicillin so far described.[35,40]

Route of administration—Reactions might be anticipated with greater frequency in patients who have received penicillin by inhalation than in those who have received it by other routes of administration. Reactions following oral administration have been much less frequent and usually less severe than those following parenteral administration.[9,35]

Occupation—Persons working in environments in which a high level of penicillin exposure occurs are particularly likely to have been sensitized to the antibiotic. Persons employed in penicillin manufacture, druggists, nurses and physicians in particular would fall in this category.[41]

Age—Reactions to penicillin seem to occur far less often in children than in adults.

Diagnostic Technics to Prevent Penicillin Reactions

A positive reaction to a skin test with penicillin so strongly suggests the presence of humoral antibodies as to preclude use of the drug.[15] We believe such a positive test result should be accepted as a contraindication despite the fact that many reports[5,42] indicate a significant number of these results may be "false positive reactions," in which cases the

patients would be deprived of the drug unnecessarily. On the contrary, a false negative result may not be infrequent, although Peters, Henderson and Prickman[42] and Feinberg and Feinberg[22] have stated that they know of no case of anaphylactoid reaction preceded by a negative skin test. A consensus of the evidence would indicate that it is desirable to perform skin tests with penicillin before any patient receives this antibiotic and that such tests are obligatory if there is truly a question of previous sensitivity. Tests to anticipate reactions to this drug are of three types.

1. Patch tests—This type of testing ordinarily is performed to determine a contact-type sensitivity, and usually a solution containing 50,000 units per milliliter is used. A positive reaction may be elicited in 24 to 48 hours.[15] This type of testing is not satisfactory for the serious reactions under consideration in this discussion.

2. Scratch, puncture and intracutaneous testing—These tests are indicated to predict the occurrence of the more serious types of reaction. Recommended concentrations of solutions to be used for the scratch or prick test vary from 0.1 to 300,000 units per milliliter.[5, 18, 22, 42] In the event that sensitivity is not suspected or the likelihood seems remote, the more concentrated solutions may be justified. However, if the possibility of sensitivity is considered seriously, we would suggest using extremely dilute solutions first, followed by tenfold increases on subsequent tests. If the scratch or prick tests with the most concentrated solutions produce negative results, intracutaneous tests with solutions containing 100 to 100,000 units per milliliter may be attempted with a fair degree of safety. The suggestion to start with extremely dilute solutions seems justified on the basis of reports of serious reactions to tests with solutions containing as little as 0.000003 unit of penicillin per milliliter.[21] While such fine degrees of sensitivity are unusual, anaphylactoid reactions to intracutaneous tests with more concentrated solutions are not uncommon in the literature.[13, 43]

3. Passive transfer tests—Use of this type of test is indicated in patients whose histories strongly suggest sensitivity of such extreme degree that even scratch testing with dilute solutions would be hazardous.

Therapeutic trial—In doubtful cases in which the past history and results of skin testing are not clear-cut, it seems justified to administer a very small amount of the antibiotic.[24, 42] Brown[24] suggested the following procedure: (1) Give an oral antihistamine, followed in 15 minutes by (2) 0.3 ml. of 1:20 epinephrine in suspension injected into separate sites (for adults); (3) to the penicillin dosage, add half a dose of injectable antihistamine and another 0.1 to 0.3 ml. of 1:1000 aqueous epinephrine (for adults); (4) inject one-third of the dose into the lower arm and the remainder divided into two doses given 20 to 30 minutes apart.

When penicillin sensitivity is strongly suggested, it is obvious that the procedures outlined may be extremely cumbersome for the busy physician who may be unable to devote the time necessary to perform them. It would then seem wiser to refer the patient to a physician prepared to perform the procedures as a daily routine. No effort is too great to protect the safety of the patient.

Other Necessary Steps in the Administration of Penicillin

In addition to the precautions already outlined in regard to inquiry into the past history and to skin testing, due care must be exercised in the parenteral administration of penicillin. Great care is necessary to avoid administering the drug intravenously.[44] Small-gauge needles should be used, with at least two withdrawals of the plunger during the course of injection. Firm pressure then should be applied over the site for at least one minute to prevent intravenous seepage. Re-emphasis of these points seems indicated in view of the tendency to haste when attempting an injection, particularly in a small but vigorously protesting child. After the penicillin is administered, the patient should be watched carefully in the office or home for at least 15 minutes. Emergency equipment certainly should be available in the event of a reaction. It would seem desirable to have a syringe full of 1:1000 aqueous epinephrine available for immediate use wherever penicillin is being administered.

Treatment of Penicillin Reactions

In the event of severe anaphylactoid reaction to penicillin, death may occur so quickly that no therapy can be instituted promptly enough to prevent it. However, more often the situation is not so critical, and prompt and vigorous treatment may be the difference between life and death. The following measures are suggested in the approximate order of their importance, in our opinion.

1. Inject 0.5 ml. of 1:1000 aqueous epinephrine into the site of the injection to delay absorption, and inject 0.3 ml. into the opposite arm for therapeutic effect (adult dosage).

2. Place a tourniquet above the site of injection.

3. Maintain an adequate airway by whatever means is required, including tracheotomy for respiratory obstruction due to angioneurotic edema.

4. Place the patient in a comfortable lateral or prone position and cover him with blankets in the event of shock.

5. Use oxygen liberally to help combat hypoxia, particularly when respiratory passages are obstructed by angioneurotic edema.

6. Use vasopressor drugs when time permits; recovery or death may supervene.

7. Theophylline derivatives given intravenously may be employed, particularly if pulmonary edema is prominent.

8. Antihistamines administered intravenously may be helpful after all the measures already mentioned have been instituted, but we cannot emphasize too strongly that these agents have no place in the front line of anaphylactoid therapy.

9. ACTH and corticosteroids are much too slow in therapeutic action to be used in any manner except as adjuncts to the measures already listed. We believe this is extremely important to bear in mind, particularly in view of the claims of several pharmaceutical manufacturers regarding the use of parenteral corticosteroid preparations as a defense measure against anaphylaxis.

10. Delayed reactions are managed according to their type. In a delayed urticarial reaction, penicillinase, a bacterial enzyme commercially derived from *Bacillus cereus*, may be useful. Injected parenterally, it hydrolyzes penicillin to an antigenically inactive penicilloic acid. However, anaphylactoid reactions have been reported following the administration of penicillinase, and, further, multiple injections may be required as the penicillin may outlast the life of the enzyme.[19] Serum sickness and vasculitis may not respond to the inactivation of penicillin, and antihistamines or corticosteroids may be required for control.

Other Measures for the Control of Penicillin Reactions

Certain other measures may be desirable for the control of the immediate or delayed type of penicillin reaction.

1. A modification of the Pure Food and Drug Act would seem desirable to reduce the contamination of milk by penicillin, as described previously.

2. Identification cards should be issued to known penicillin reactors.

3. Penicillin desensitization has been suggested[45] but it would seem that this is rarely indicated in view of the extreme degree of sensitivity which may exist. Avoidance of the antibiotic would seem the wiser course.

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Detection of Ovulation

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None of the many methods to detect ovulation is infallible or entirely satisfactory; a reliable, consistently accurate, simple technic is urgently needed.

It is not possible to claim definite preference for one method, as so much depends on available facilities, experience, and diligence of application, but the author has found the serial vaginal smear to be the most valuable and accurate technic.

S. J. BEHRMAN

THE prime function of the ovary is to produce an egg each month for the purpose of fertilization. This ovulatory event is the result of an intricate, complex mechanism that has been the subject of investigation for many decades. Even today the precise minutiae surrounding this phenomenon have not been clearly elucidated. Consequently it is easy to understand why the clinical timing of ovulation is still somewhat crude and inaccurate. It is also quite obvious that the time of ovulation has great biologic and clinical significance, being of inestimable value in problems of infertility, in diagnosis and treatment of disorders of menstruation, and in suppression of fertility.

Before one can intelligently discuss methods of detection, two concepts of basic physiology require brief elaboration: the events leading to ovulation, and the actual mechanism of follicular rupture.

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Events Leading to Ovulation

Development of the follicle is under the influence of three gonadotropic hormones: follicle-stimulating hormone (FSH), luteinizing hormone (LH) and luteotropic hormone (LTH). As the gonadotropic hormones react on the ovaries, the latter in turn react on the anterior pituitary gland, leading to an orderly regulatory sequence of cyclic changes. Preliminary preparation of the follicle is by estrogen, as described by Hisaw.[1] FSH is responsible for initiating further enlargement of the follicle after the estrogen has primed the granulosa cells and possibly the theca as well. With follicular enlargement, the estrogen produced in the follicle gradually causes the pituitary gland directly or indirectly to begin secreting

luteinizing hormone. Under the influence of FSH and LH the follicle rapidly increases in size, producing more follicular fluid. This is the short "preovulation phase" which terminates in rupture of the follicle or the phenomenon of ovulation.

According to Fevold,[2] LTH accelerates luteinization of the theca interna, but it is not yet quite clear whether LTH is necessary for the immediate phenomenon of ovulation. This is an important point, but because of our present lack of knowledge we must assume that it is the synergistic action of FSH and LH that is the trigger mechanism for ovulation. Thus, although the presence of LH does not necessarily mean that ovulation will occur, certainly the absence of LH precludes ovulation. This is the reason for the current interest in LH in relation to ovulation.[3]

Concomitant with these hormonal changes, definite physical changes occur within the cervical secretion. It becomes less viscous, the amount increases, it becomes clear of debris and leukocytes, it is more bacteriostatic and exhibits the rheologic properties of spinnbarkeit, and often crystallization or "fern" formation occurs. The latter indicates increased receptivity to spermatozoal penetration.

Mechanism of Follicular Rupture

The precise mechanism of follicular rupture is not clearly understood, but many theories have been advanced.

1. Increase of intrafollicular pressure.
2. Hyperthermia and blood pressure changes.
3. Excess secretion of follicular fluid.
4. Effect of a proteolytic enzyme.
5. The theory of tropism propounded by Strassmann.[4]
6. A possible morphologic change in the follicular stigma, of unknown cause and nature.
7. Barjaktarovitch[5] stated, "It is believed that when the intrafollicular pressure rises to a maximum as a result of the action of pituitary gonadotropins, the nerves to the theca are stimulated and this results in stimulation of the pituitary. The latter produces not only LH, but also the oxytocic hormone of the posterior lobe which causes contraction of the follicle. Under the influence of these contractions, similar to those of the gravid uterus, the follicle bursts, the connections between the corona radiata are ruptured and the ovular contents is expelled."

Not only are the events leading to the phenomenon of ovulation and the mechanism of actual rupture obscure, but culdoscopic observations by Decker[6] indicate that actual rupture of the follicle is not always an explosive phenomenon; a minute, hours or days may be required for the ovular contents to escape. The variability of the thermal shift of the basal body temperature seems to testify to this. The shift may occur rapidly over 24 hours or slowly over several days, depending perhaps on whether expulsion of the ovum is rapid or slow. In any event, while the temperature chart is a useful retrospective tool to indicate whether or not ovulation has occurred, it is not an accurate means of predicting ovulation prospectively. Nor is it possible, in my experience, to say whether ovulation occurred at the low, mid or high point of the thermal shift. One thing is sure, however, and that is that ovulation cannot be forecast by using the mythical day 14 of the menstrual cycle. In a recent study[7] of successful artificial insemination where only a single injection of semen was made, it was determined that only 30 per cent success was obtained on day 14; in the remaining 70 per cent of cases the day of successful injection varied from day 8 to day 21.

The wide variation of time of ovulation among different women combined with the fact that there may be a two to three day variation in successive cycles in the same woman make it abundantly clear that an easy, inexpensive, rapid and accurate method to detect ovulation is required. Moreover, most of the tests to detect ovulation today become positive only *after* the event has occurred, which may be too late or make the test valueless. What is needed is a test that will *predict* ovulation, and this is perhaps the goal we should strive for.

Methods to Detect Ovulation

In recent years, several excellent reviews of methods to detect ovulation have been published,[8-10] and there have been some new de-

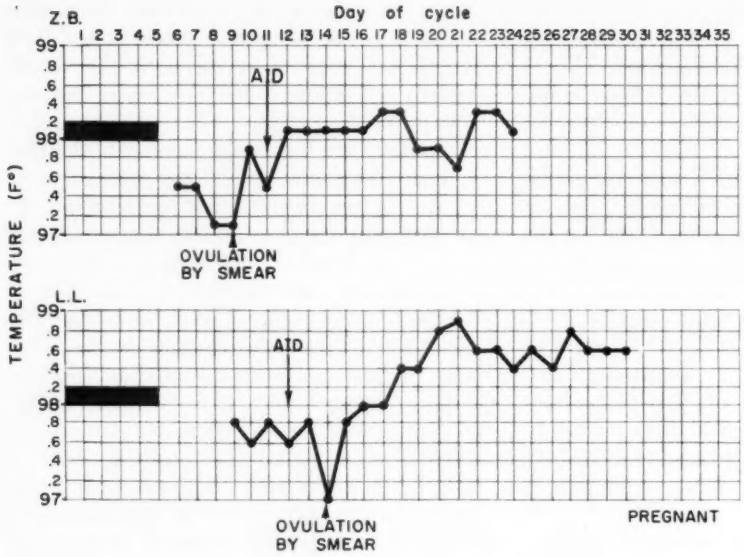
Z.B.
Day of cycle
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
TEMPERATURE (F°)
AID
OVULATION BY SMEAR
L.L.
AID
OVULATION BY SMEAR
PREGNANT

FIGURE 1. Two examples of successful impregnation by a single insemination (AID) 36 hours before and 36 hours after ovulation was predicted by the vaginal smear technic.

velopments in this field. Summarizing these to date, it appears that the various methods almost automatically divide themselves into two categories.

Positive methods—The only true method of positive proof of ovulation is the establishment of pregnancy or direct observation of ovulation through a culdoscope or at laparotomy.

Presumptive methods.

1. Endometrial biopsy.
2. Basal body temperature chart.
3. Exfoliative cytology, e.g., Papanicolaou vaginal smear.[11,12]
4. Studies of cervical mucus, e.g., spinnbarkeit,[13] fern tests.[14,15]
5. Electropotential changes.[16-18]
6. Midcycle pain (mittelschmerz).
7. Midcycle bleeding or staining.
8. Use of glucose-reducing reagents as proposed by Birnberg and associates[19] and Doyle.[20]
9. Estimation of hormonal levels, i.e., pregnanediol, gonadotropin levels,[21] Farris test.[22,23]
10. Sevag's[24] biochemical test.
11. Evaluation of blood platelets.[25]

Discussion

Evaluation of the practicality or value of these methods must be approached with due consideration to availability of laboratory facilities and in the light of one's own experience and that of others. Further, it should be appreciated that enthusiastic reports of "success" with any particular technic based on an ensuing pregnancy are accurate only within certain limitations. Realizing that the ovum may survive for 12 to 24 hours and the spermatozoa for 12 to 72 hours under ideal circumstances, it is indeed possible that pregnancy may result at any time from 12 to 72 hours after or even 12 to 24 hours before the predicted time of ovulation (figure 1).

Bearing this variant in mind, it becomes even more apparent why a method is needed whereby one could narrow down the time of ovulation to within 12 to 24 hours and, ideally, *predict* this event a day or two before it occurs. Only the Farris test and the Sevag biochemical method permit any prediction of ovulation.

The Farris test is based on a hyperemic response of a rat's ovaries to the intraperitoneal injection of urine (morning specimen), and takes four hours to complete. Although its validity has been questioned, a modification devised by us and used by Dresner and Cohen[26] has given fairly good (75 per cent) correlation. Even more important, it has the advan-

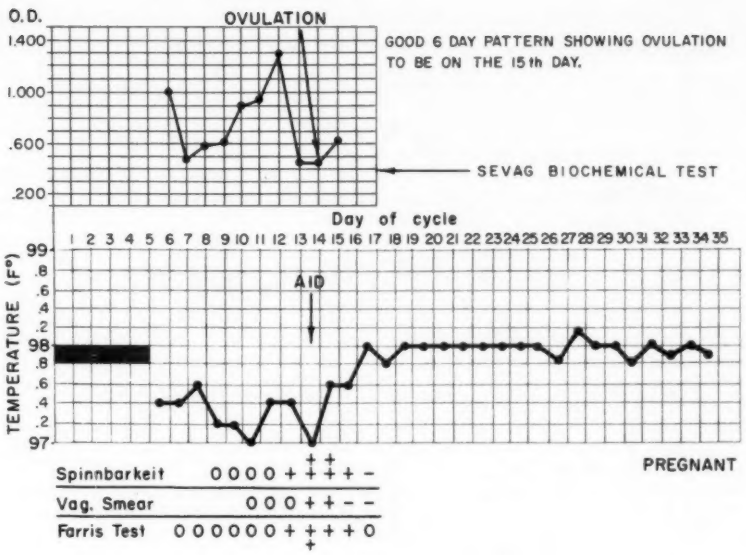
O.D.
OVULATION
1.400
1.000
.600
.200
GOOD 6 DAY PATTERN SHOWING OVULATION TO BE ON THE 15th DAY.
SEVAG BIOCHEMICAL TEST
Day of cycle
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
TEMPERATURE (F°)
99
.8
.6
.4
.2
98
.8
.6
.4
.2
97
AID
PREGNANT
Spinnbarkeit 0 0 0 0 + + + + –
Vag. Smear 0 0 0 + + – –
Farris Test 0 0 0 0 0 0 + + + + + 0

FIGURE 2. A pregnancy resulting from a single insemination (AID). Note the close correlation between the Sevag biochemical test, the modified Farris test, the vaginal smear and spinnbarkeit.

tage of becoming weakly positive a day or two before the correlation point, at which time it is strongly positive. Thus it gives a day or two of warning before actual ovulation occurs, and this feature is particularly valuable in artificial insemination. We believe the Farris test is an indication of increased amounts of luteinizing hormone, as confirmed by the technic of Witschii.[27]

The biochemical test of Sevag also has this advantage of predicting ovulation. It is based on color development of morning urine specimens over a period of five to six days, wherein a pattern of chemical values offers a basis of prediction. The efficacy and accuracy of the test remain to be confirmed, but in a few cases in which we have attempted it in our laboratory it has shown excellent correlation with other tests (figure 2). Unfortunately, such tests and the estimation of hormonal levels require elaborate laboratory facilities and thus are unavailable to most physicians.

By far the most widely used clinical methods of detecting and timing ovulation are the basal body temperature chart, the vaginal smear, and the endometrial biopsy. The variability of the basal body temperature chart makes prospective timing of ovulation extremely difficult, inaccurate and therefore unreliable (figure 3). The real value of the temperature chart is that one can say, in retrospect, that ovulation did in fact occur and can state roughly the time of its occurrence. It is then possible to predict, within two or three days, the day of ovulation of the next cycle.

Correlation of the endometrial biopsy with ovulation is quite accurate, but as a day-by-day or routine technic it is impractical and inadvisable because of the possibility of dislodging an already existing pregnancy.

We have found, as have others,[11,12] that the vaginal smear is an extremely useful method in experienced hands because of the sharp change visible on the day of ovulation. The method does have the disadvantage of requiring an expert cytologist. In a well-run laboratory the technic permits the patient to bring in smears daily by 9:00 A.M. and have the result by noon.

Midcycle pain or bleeding is so variable a symptom as to preclude its usefulness. Similarly, electropotential changes and platelet counts cannot at this time be considered practical methods.

The most practical approach for the clinician appears to be a study of the cervical mucus, which requires no apparatus or laboratory facilities at all. However, it, too, is subject to

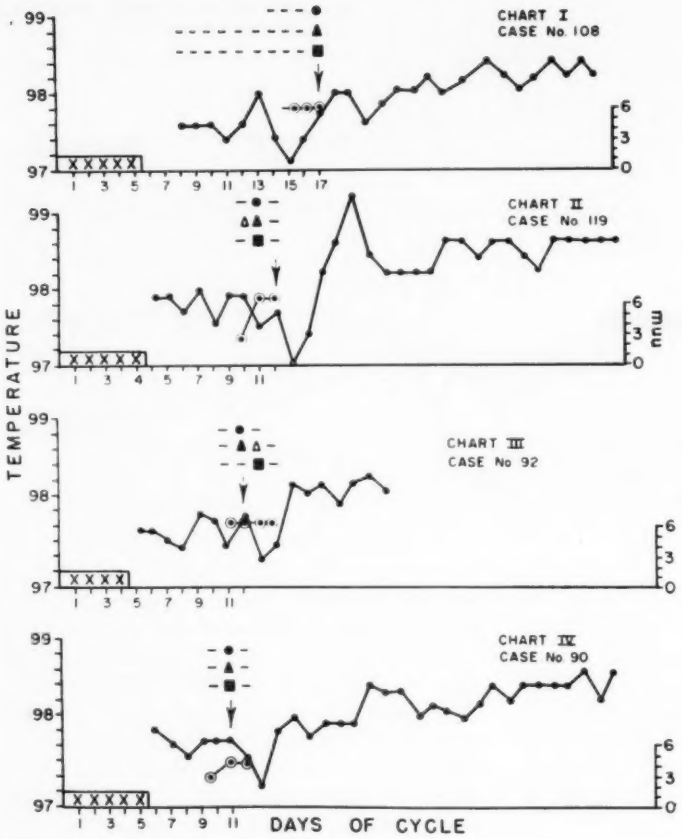

FIGURE 3. Several examples of successful pregnancy obtained following a single insemination (arrow). Again note the close correlation of predicted ovulation between the serial vaginal smear (■), the modified Farris test (▲), and maximal spinnbarkeit (●); note also the lack of correlation between these technics and the thermal shift of the temperature chart.

certain shortcomings. A common error is the idea that crystallization or ferning of the mucus indicates ovulation. It merely indicates receptivity of the mucus to spermatozoal penetration. Ferning of the mucus occurs at the peak of estrogen production, which coincides with the time of ovulation. It is possible to induce this phenomenon in oophorectomized women, who obviously cannot ovulate, by merely giving oral estrogen. Conversely, even in the presence of ovulation the cervical secretion may not show any ferning, either because the level of endogenous estrogen produced is insufficient or because there is considerable infection of the cervical glands. Therefore, it is important to realize that while ferning is required for sperm penetration, and that it is most typically found at the time of ovulation, it is not a reliable indication per se of ovulation. Spinnbarkeit, on the other hand, is a very valuable, easy and practical method in the hands of anyone willing to collect the cervical mucus, put it between two cover slips, and test the "stretchability" or elasticity of the mucus; it is maximal on the day of ovulation (figure 2).

Recently a pretreated applicator has been devised[19,20] which, when inserted in the cervical canal at the time of ovulation, will reduce the glucose present in the cervical secretion and show a color change. While such a simple technic would be ideal, the variability of results obtained by many workers to date indicates that further study and refinement are required before it can be considered sufficiently accurate or practical for general use. This same criticism applies to the tampon or TESTAPE® technics.

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Changing Emphasis in Chest Film Survey Procedures

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Selective extension of chest film survey procedures will aid greatly toward the clinical conquest of tuberculosis, neoplasm, and cardiovascular and degenerative disease.

Special attention should be given to surveys of registrants at hospitals and clinics, coverage of young adults by college and pre-employment surveys, periodic examination of industrial workers and elderly persons, and intensification of survey efforts in men over 40 years of age.

Somatic exposure to radiation can be reduced to a completely safe level; intensive effort is needed to acquaint physicians and lay persons with the desirability of continuing properly conducted surveys.

THE many changes in the practice of medicine which have taken place in the two decades since the initial development and advocated use of chest survey procedures have resulted in changing areas of emphasis in their application, the definition of their objectives, and the prospective candidates to whom they should be applied. The most significant as reflected in these changes in emphasis might be listed as follows.

1. The declining mortality rates and, in some areas, the declining incidence of active pulmonary tuberculosis.

2. The increasing incidence of bronchial neoplasm, together with a growing appreciation of the natural history of bronchial carcinoma and its early roentgenologic signs.

3. The technical advances in thoracic surgery, enabling more prompt and thorough investigation of mediastinal and parenchymal neoplasm or lesions in which neoplasm cannot otherwise be excluded.

4. The technical advances in diagnostic procedures, anesthesia, and methods of cardiac surgery, which call for prompt recognition of cardiovascular lesions amenable to therapy.

5. The realization by industry of the importance of adequate pre-employment baseline studies, both from the standpoint of the worker's health and to protect industry against unjust compensation claims.

6. The recognition of the statistical validity

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of studies relating to the fallibility of interpretation of survey films by a single reader.

7. The now receding wave of public hysteria concerning exposure to radiation and the extended education of medical personnel concerning radiation precautions.

To what extent are these considerations for changing the emphasis in chest surveys valid, and how shall we incorporate the resultant modifications in our current and projected survey procedures?

Tuberculosis

At the time of their inception and early application, chest survey procedures were justified almost entirely as a means of tuberculosis case finding. The yield of surveys of the general population, of persons admitted to hospitals, and of occupational groups was sufficient to justify this emphasis. The hospital registration survey in particular was justly advocated as a major step in the protection of hospital personnel from unrecognized active tuberculosis and in enabling more prompt recognition of the necessity for therapy.

For example, in 1949 a review of a survey of registrants at The University of Michigan Hospital and Clinics indicated that recognizable tuberculosis other than calcified foci or nodes was found in 3.2 per cent, with 1.28 per cent eventually showing active tuberculosis.[1] A similar sampling during the year from 1954 to 1955 yielded an estimated incidence of active tuberculosis among registrants at The University of Michigan Medical Center of 0.14 per cent.[2] It should be emphasized that in the state of Michigan at large the incidence of newly reported active cases has shown no such decrease, although increasingly effective methods of treatment have resulted in a marked decrease in duration of hospitalization, a more rapid turnover of patients, and increasing sanatorium bed vacancies. As a consequence, the general public has an exaggerated view of the progress that has been made toward elimination of this disease as a public health problem. Actually the decreasing incidence of the disease presents a challenge to develop more efficient survey methods to find the remaining cases so that these persons too may have the advantages of modern chemotherapeutic and surgical methods.

The growing number of older persons in our population has emphasized the urgency of adequate coverage of these persons as the trend in tuberculosis from a disease of younger people to a disease of old age has been recognized. The tendency of latent tuberculosis to become active in older persons with the stress of other degenerative and debilitating disease must be constantly kept in mind in the screening and subsequent management of persons admitted to hospitals.

Solely from the standpoint of tuberculosis case finding, then, the following emphasis in survey procedures seems justified.

1. The decreasing incidence of tuberculosis increases the effectiveness of the tuberculin skin test as a diagnostic tool, and this rather than chest filming should be utilized in grade school and high school populations. Chest filming should be reserved for positive reactors to skin testing.

2. While it appears that the incidence of active tuberculosis among persons admitted to hospitals is decreasing, prompt detection of the active cases by survey procedures remains a prime consideration both to protect hospital personnel and because of the many advantages of early recognition and therapy.

3. Surveys of the general population are far less efficient as tuberculosis case-finding procedures.

4. It is increasingly urgent to survey the aging segments of the population, both to institute prompt therapy and to obliterate a reservoir for transmission of the disease.

Intrathoracic Neoplasm

One of the frustrating paradoxes of current medical practice lies in the increasing incidence of bronchial neoplasm and the inability of thoracic surgeons, chemotherapists and radiologists to effect a satisfactory percentage of cures in spite of many recent technical advances in these fields. Considerable pessimism has been expressed concerning the wisdom of extensive chest surveying for this lesion when so little in the way of tangible long-term results can be achieved. It seems probable that biologic behavior of the neoplasm influences the eventual survival period more than does promptness of roentgenologic recognition. There are, however, some data to indicate that asymptomatic lesions detected incidentally in survey films do have a better prognosis than do lesions discovered otherwise. Regardless of the facets of biologic predeterminism implied in tumors so discovered, it seems reasonable that their prompt removal will contribute to an improvement in the eventual cure rates, although the more aggressive symptomatic lesions may continue to be difficult to manage. Many of the asymptomatic lesions have spread beyond control.

Discouraging though the outlook may be with current diagnostic and therapeutic methods, it does not seem that a fatalistic, nihilistic attitude is to be preferred. An aggressive neoplasm necessitates an intensified, aggressive diagnostic approach. Intensive studies of extended surgical, chemotherapeutic and radiologic technics can be expected to show some progress. Should an unexpected therapeutic "breakthrough" be accomplished, efficient chest survey procedures would be indispensable to enable patients to profit promptly thereby. Even with currently feasible extensions in survey technic it is not impossible that improvement in survival with current therapeutic methods can be achieved. Such aggressive extension of survey technic deserves at least a statistical evaluation of its effectiveness.

Thanks to the emphatic teaching of Rigler[3] and others, the earliest roentgenologic signs of bronchial neoplasm are more widely understood, and it is toward this early recognition that future survey filming must be aimed. Both localized parenchymal lesions and early disturbances in bronchial dynamics must be recognized in more subtle manifestations and with a higher index of suspicion. Men over 40 years of age must be subjected to more intensive survey procedures than other groups. To accomplish this, it is currently being proposed at The University of Michigan Medical Center that the admission survey chest filming be extended for men over 40 to include in addition to a frontal 70 mm. photofluorogram a lateral view in inspiration and a frontal view in expiration. It is thus hoped that recognition of the earliest roentgenologic signs will increase, and, in any event, data for the statistical evaluation of the effectiveness of this extension will be gathered.

In situations where men in this age group are fairly stable and available for continued observation, such as in industry, in the armed services, and in veterans hospitals, aggressive extension of periodic examinations will provide for large-scale evaluation of the possible increase in cure rate which may result.

While bronchial neoplasm is the most urgent problem of neoplasm in relation to chest survey filming, we must not overlook the importance of other neoplasms. Recognition and removal of mediastinal tumors continue to be important, and we believe this facet is a significant part of the reasoning behind the continuation of chest film admission surveys of college students and other young adults in preemployment and hospital registration procedures. Other benign and malignant pulmonary lesions will be demonstrated subsequently, as their absolute identification requires their removal; technical advances in thoracic surgery now permit this aggressive approach to otherwise unidentifiable pulmonary and mediastinal lesions.

From the standpoint of intrathoracic neoplasm we may conclude that (1) intensification of survey efforts in men over 40 years of age is urgently needed, in terms of extension of technics of surveying, inclusion of larger numbers of the older male population, and periodic re-examination, and (2) we should continue to encourage surveys of young adults

at the college and pre-employment levels to find otherwise unidentified mediastinal and pulmonary abnormalities, some of which will prove to be benign, potentially malignant or malignant neoplasm.

Cardiovascular Abnormality

The revolution in intrathoracic surgical technics has included many advances in cardiovascular surgery. Many of these technics are being applied to symptomatic cardiac lesions in infancy and childhood. However, there are many adults who have relatively asymptomatic, correctable lesions such as coarctation of the aorta, patent ductus arteriosus, and septal defects which are better treated before complications or irreversible pulmonary changes occur. It is this group of patients which it is important to identify in surveys of young adults such as college students or persons covered by pre-employment surveys.

Acquired cardiac lesions are more likely to produce symptoms and to come to the attention of the clinician, but in this group too occasional cases not under medical supervision will be discovered and the eventual aid of cardiac surgery made possible. In the older age groups attention can be called to cardiomegaly, pulmonary congestion, and pericardial and pleural abnormality, and thus the patients may be placed under medical supervision more promptly than they would if symptoms were the only consideration.

The results of the 1955 mobile x-ray survey of the Wisconsin State Board of Health are of interest in this regard.[4] From 129,894 chest films (70 mm.) there were 3,477 referrals of patients to private physicians for cardiovascular disease. The presence of heart disease was confirmed in 1,904; 4.8 per 1000 had previously known heart disease, and 9.8 per 1000 had verified heart disease which was not previously known.

From the standpoint of cardiovascular disease, therefore, it is desirable to consider three groups of patients: (1) those with previously undiagnosed congenital abnormalities, (2) those with rheumatic heart disease, which is best treated surgically before secondary changes progress too far, and (3) those with cardiomegaly or evidence of congestive failure whose discovery will permit earlier institution of appropriate therapy. It appears that surveying of young adults is justified by the first two considerations and that periodic examination of persons in the older age groups would satisfy the third.

Industrial Hygiene

Among the recent important advances in medicine is the enlightened interest of industry in the welfare of its workers. The relationship of the plant physician with the worker's private physician has improved. Occupational hazards have been studied more thoroughly and eliminated more effectively. Industry sees the importance of thorough pre-employment base-line studies to protect itself from unjust compensation claims. Industries in which any possibility of hazard exists are realizing the necessity of periodic re-examination.

The pre-employment chest survey not only satisfies the industrial requirements but serves as well to insure partial coverage of the young and middle-aged adult population for other nonindustrial diseases. The periodic re-examinations in industries with dust hazards serve the ends of the search for neoplasm in men over 40. Inasmuch as nearly all industrial medical departments are equipped for rapid chest filming, it is suggested that they might consider offering their employees periodic re-examination, annually for all and semiannually for men over 40, so that the other medical goals of chest surveying can be achieved in addition to the strictly industrial objectives.

Survey Film Interpretation

The problem of satisfactory interpretation of survey films, particularly in regard to the more subtle changes in the recognition of early roentgenologic signs of disease, has engaged the attention of radiologists and statisticians for more than two decades. Garland[5] reported a variation of 9 to 24 per cent in interpretations by different readers and a variation of 3 to 31 per cent for the same reader. Zwerling and associates[6] concluded that the problem of error in interpretation of chest films in mass radiographic surveys is of extreme practical

importance and can be minimized to some extent by having films read by more than one reader.

Bauer[7] recently re-evaluated in detail the problem of reliability of film interpretation. He tested eight readers with a series of 3,268 photofluorograms, among which the films of 99 persons with clinically verified active pulmonary lesions were distributed. Single reading resulted in an adequate evaluation of an average of 61 per cent of test cases. Independent dual reading followed by consultation of the readers on their differences improved the results to an average of 76 per cent. Excellence of individual performance is variable and to a degree related to experience. While dual reading more than doubles the professional time required for interpretation, the increased yield justifies the investment; false economy in the final phases of film interpretation and follow-up may well vitiate the entire program.

Radiation Hazards

A by-product of the era of atomic energy has been the widespread public discussion of radiation and its hazards. As the largest contributor to artificial exposure of persons to radiation, the medical use of x-rays has been rigorously re-evaluated. Unfortunately in some cases the concern of patients has led them to refuse x-ray examinations for which there was good indication. Because of the potentially large number of persons involved, survey chest filming has come in for its share of criticism.

Important dividends of this public concern about radiation exposure have been the necessity for radiologists to re-examine the provisions they have made to reduce such exposure to a minimum necessary for adequate filming, a re-emphasis on gonadal protection, and the desirability of informing the patients of the necessity for continued adequate use of diagnostic radiology on sound clinical indication.

All survey equipment should have the basic 3 mm. aluminum filtration and appropriate limitation of the beam by lead diaphragms. The fastest available film consistent with good diagnostic detail should be used. As soon as it is financially feasible, lens optic cameras should be replaced with mirror optics. With high-kilovoltage technics and appropriate increase in distance between tube and subject, it is felt that sufficient reduction in radiation is achieved to justify the continued widespread use of survey filming.

Discussion and Summary

The influence of various changes in medical practice in relation to survey chest filming has been indicated. These considerations can be integrated to see which population groups should be given special attention.

It has been our experience that neonatal chest surveying is of little value. As carried out with routine 8 by 10 in. films over a period of several years, the only abnormalities detected were those to which attention would have been called on clinical grounds. In young children, survey photofluorography is difficult because of lack of cooperation, and at The University of Michigan Medical Center this procedure has been eliminated for children less than five years old. Routine large films are obtained if otherwise indicated, with appropriate gonadal protection.

Patients registering at general hospitals and clinics continue to be a fruitful source for significant survey findings. The most recent tabulation at The University of Michigan Medical Center showed the incidence of suspected significant abnormality to be 7.4 per cent of the registrants; 80 per cent of these proved to be significant. The estimated incidence of intrathoracic neoplasm (0.56 per cent) now exceeds that of active tuberculosis (0.23 per cent). Approximately 75 per cent of the significant thoracic abnormalities found were not directly related to the reason for the patient's referral to the hospital or clinic. In our opinion, continuation of hospital survey filming is indicated for all patients more than five years old.

Survey filming of children in elementary and high schools seems justified only as a limited supplement to tuberculin skin testing. Coverage of young adult population groups by college and pre-employment chest surveys is justified to detect congenital abnormalities, mediastinal masses, acquired cardiovascular disease, and active pulmonary disease and as

a valuable base-line for reference should intrathoracic abnormality arise in the future.

Periodic examination of industrial workers exposed to hazardous environment continues to be necessary, both to protect the worker and for the medicolegal protection of the employer. Extensions of chest surveys among middle-aged and older men are urgently needed to see if an improvement in the cure rate for bronchial neoplasm can be so achieved. Evaluation of a semiannual routine checkup should be carried out on a broad basis.

In view of the significant increase in incidence of tuberculosis among older persons, facilities should be extended to survey this group periodically, possibly as part of the "senior citizen" programs. Early recognition of acquired cardiovascular disease and its complications would thus also be facilitated.

All possible efforts should be made to reduce the radiation exposure incident to survey procedures, including transition from lens optics to mirror optics in photofluorographic cameras. It should be emphasized that gonadal exposure is of little significance in middle-aged and older age groups, that adequate gonadal protection can be assured in younger age groups, and that somatic exposure can be reduced to a level of complete safety. Because of the persistent public concern about hazards of radiation, intensive educational efforts should be made to acquaint physicians and lay persons with the desirability of the continuation of properly conducted survey procedures. It is suggested that voluntary health organizations such as the tuberculosis, heart and cancer associations might well undertake jointly this educational effort.

While the complete population surveys which are feasible in some regimented health systems in Europe seem neither feasible nor entirely desirable in the more decentralized American systems, it is apparent that selective extension of survey procedures is both desirable and feasible.[8] Participation and cooperation of public health agencies, hospitals, educational institutions, industry and voluntary health organizations in addition to private physicians will be necessary for optimal coverage. Further progress in the clinical conquest of tuberculosis, neoplasm, and cardiovascular and degenerative disease will be aided greatly by such selective extension of these technics.

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Diffuse Interstitial Fibrosis of the Lung

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Three examples of arbitrarily defined clinical patterns of diffuse interstitial fibrosis of the lung are presented from a series of 10 pathologically established cases. These cases, as well as 12 others diagnosed on presumptive clinical evidence, are discussed with respect to etiologic concepts. The problems of clinical diagnosis and the importance of differential diagnosis are outlined. Emphasis is placed on clinical criteria for diagnosis, particularly the unusual character of the rales.

MANY of the problems relating to diffuse interstitial fibrosis of the lung (Hamman-Rich syndrome), including confirmation of the diagnosis, remain in the province of the pathologist. However, observation of increasing numbers of patients with this syndrome has established certain reliable diagnostic criteria which allow the clinician to make the diagnosis with considerable authority.

Diffuse interstitial fibrosis of the lung is not uncommon. I shall describe in some detail three cases in which the diagnosis was confirmed and discuss 19 other cases.

Since 1954, eight cases substantiated by autopsy and two cases diagnosed by biopsy of the lung have been studied by the Medical Chest Unit of The University of Michigan Medical Center. In the 12 other cases, all the clinical criteria necessary for diagnosis were met but pathologic proof is lacking. These 22 cases are not indicative, however, of the total experience with this disease at the University Hospital.

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Classification

It appears possible to delineate, in an arbitrary fashion, three separate clinical patterns of diffuse interstitial fibrosis of the lung: acute, chronic and subacute. This classification is based on temporal and pathologic factors, realizing that pathologic changes do not always parallel the passage of time. We suggest that when the symptoms and signs are acute and the duration of illness is six months or

less the disease be considered *acute*. At the other extreme is a *chronic* course lasting two years or more. Classed as *subacute* is a form of the disease with symptoms and total duration between acute and chronic.

Case Reports

The spectrum of diffuse interstitial fibrosis is evident in the three cases to be described, as are certain clinical and pathologic features of the syndrome.

Case 1—A 52 year old white man was thought to be in good health except for fatigue attributed to overwork until June 14, 1954, when a cough and hoarseness developed. These symptoms progressed but did not interfere with his busy schedule until June 24 when he was hospitalized with findings suggesting pneumonia. Two and a half hours after admission he had an acute episode of dyspnea, cyanosis and peripheral vascular collapse suggesting myocardial infarction, for which he was treated, although subsequently this diagnosis was not substantiated. Over the next four weeks his clinical condition fluctuated but he remained dyspneic, febrile and bedridden despite treatment with digitalis, diuretics, oxygen and multiple antibiotics.

Initially, roentgenograms of the chest demonstrated bilateral "pneumonia," more extensive on the right side. Within a few days the roentgenologic appearance suggested pulmonary edema or "uremic lung," and these were the diagnoses being considered when the patient was transferred to University Hospital on July 18, 1954 (figure 1).

The man was acutely ill, anxious and dyspneic. Temperature was 100.8° F., pulse rate was 110, and respirations numbered 34 per minute. Blood pressure was 122/84 (right arm, recumbent). Cyanosis on mild exertion was noted. Clubbing was not present. Crackling rales were heard at both lung bases. The heart was enlarged to percussion. A harsh systolic murmur heard at the apex was transmitted to the axilla and left subscapular area. The liver edge was felt 5 cm. below the right costal margin and was tender. There was no peripheral edema.

The value for hemoglobin was 13.5 gm. per 100 ml., the erythrocyte count 4,700,000, hematocrit reading 42 per cent, and leukocyte count 15,350 (82 per cent polymorphonuclear leukocytes, normal proportion of eosinophils). Results of liver function studies were normal. Total serum proteins measured 6.4 gm. per 100 ml. (albumin 4.1, globulin 2.3 gm.). Cold agglutinins were not present. Serum electrolytes were normal except for a venous carbon dioxide-combining power of 51 vol. per cent. Skin tests with tuberculin, histoplasmin, blastomycin and coccidioidin were negative, and sputum cultures were negative for any significant pathogens; *Candida albicans* and *Hemophilus influenzae* were present. Sputum cultures for acid-fast bacilli subsequently proved negative.

The patient was given penicillin, aminophylline, mercurial diuretics and continuous oxygen. He died suddenly on July 20, 36 hours after admission.

At autopsy the right pleural cavity contained 600 cc. of clear fluid partially loculated by delicate fibrous adhesions. The left pleural cavity did not contain adhesions or excess free fluid. The lungs were approximately twice the normal weight (990 and 940 gm.). The parenchyma was diffusely nodular to palpation, and the cut surfaces, from which a slight amount of fluid could be expressed, were deep pink with mottled patches of gray to yellow.

Microscopically the alveolar septa were thickened, with infiltration of numerous mononuclear cells, occasional polymorphonuclear leukocytes, and widespread areas of fibroblastic proliferation. The alveoli contained abundant fibrin deposited in a pattern of "hyaline membranes," and there was minimal edema with areas of focal hemorrhage. Occasional alveoli contained clusters of large macrophages. A few foci of proliferated bronchiolar epithelium were encountered (figure 2).

The total duration of this man's illness was six weeks. The onset suggested bacterial or viral pneumonia. Cor pulmonale developed, but clubbing did not. This case corresponds closely to the original description of Hamman and Rich.[1]

Case 2—A 69 year old man noted the onset of progressive exertional dyspnea in 1955.

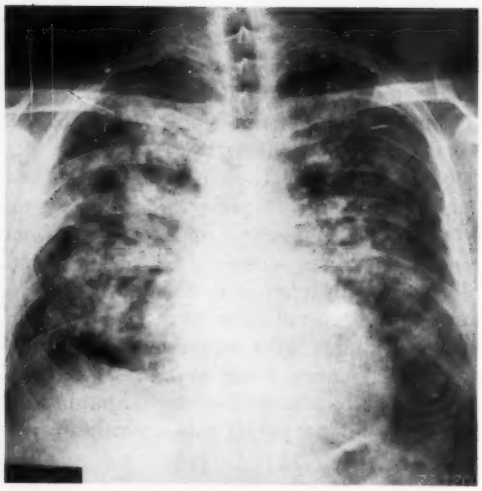

FIGURE 1. Case 1. Acute diffuse interstitial fibrosis of lung. Cardiomegaly and bilateral perihilar infiltration with tenting of right hemidiaphragm.

Chest pain typical of angina pectoris also developed. It was relieved by rest and more promptly by nitroglycerin. He experienced attacks of cough productive of small amounts of mucoid sputum, slightly streaked with blood on two occasions. Between 1955 and May 1956, when he was admitted to University Hospital, he lost 30 lb. and was nearly bedridden from dyspnea.

Mild diabetes had been diagnosed in 1954, but insulin was not required for control. He had had "pleurisy" at the age of 21 years. He smoked cigars only.

Physical examination demonstrated an elderly, dyspneic man. Blood pressure was 110/90. The pulse rate was 86 per minute. Rales were heard at both lung bases posteriorly. Clubbing of fingers and toes was noted, as well as cyanosis of the nail beds and mucous membranes. There was no peripheral edema

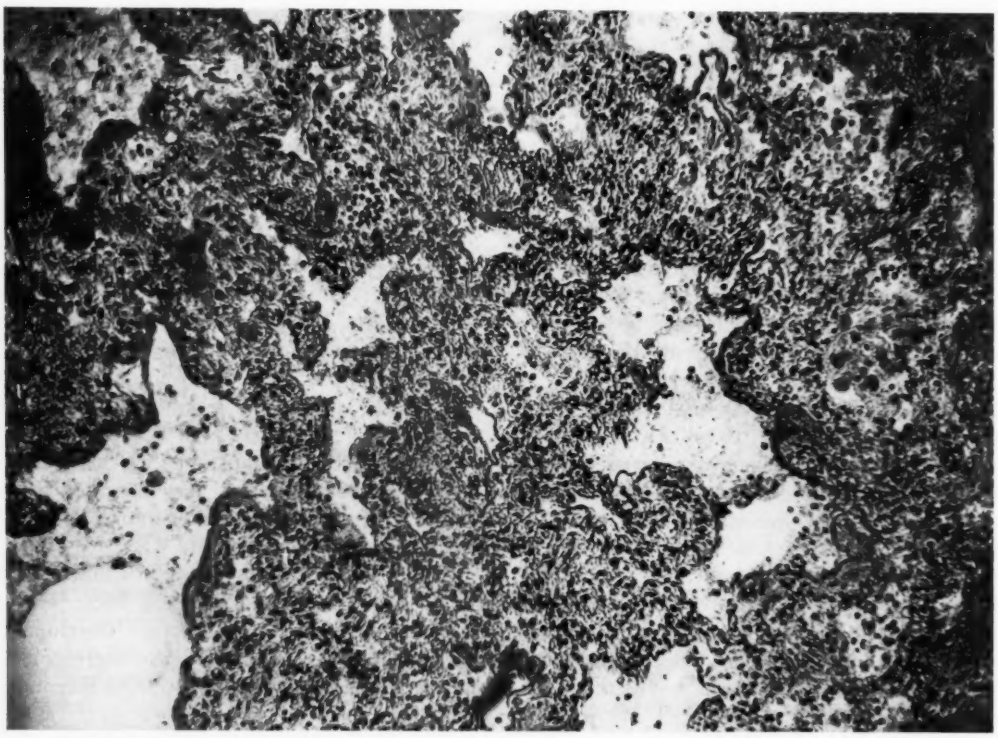

FIGURE 2. Case 1. Alveolar septa are widened and infiltrated by mononuclear cells and show diffuse fibroblastic proliferation. Alveoli contain occasional leukocytes and minimal fluid and are lined by prominent hyaline membranes.

or liver enlargement. The heart was of normal size. No murmurs or friction rub was heard. Other physical findings were within normal limits.

The hemoglobin value was 15.3 gm. per 100 ml., hematocrit reading 48 per cent, and leukocyte count 8,650 (74 per cent polymorphonuclear leukocytes). The urine and stool were normal. An electrocardiogram suggested nonspecific myocardial changes. Bronchoscopic examination demonstrated a normal tracheobronchial tree. Results of sputum tests for acid-fast bacilli, pyogens, fungi and malignant cells were negative. The fasting blood sugar level was 118 mg.

Roentgenograms of the chest made in April 1955 demonstrated extensive bilateral linear and nodular densities, and roentgenologic examination at University Hospital in May 1956 showed no change (figure 3). Biopsy of a

FIGURE 3. Case 2. The pattern of fibrosis is patchy and uneven. The roentgenologic picture is not consistent or diagnostic in diffuse interstitial fibrosis of the lung.

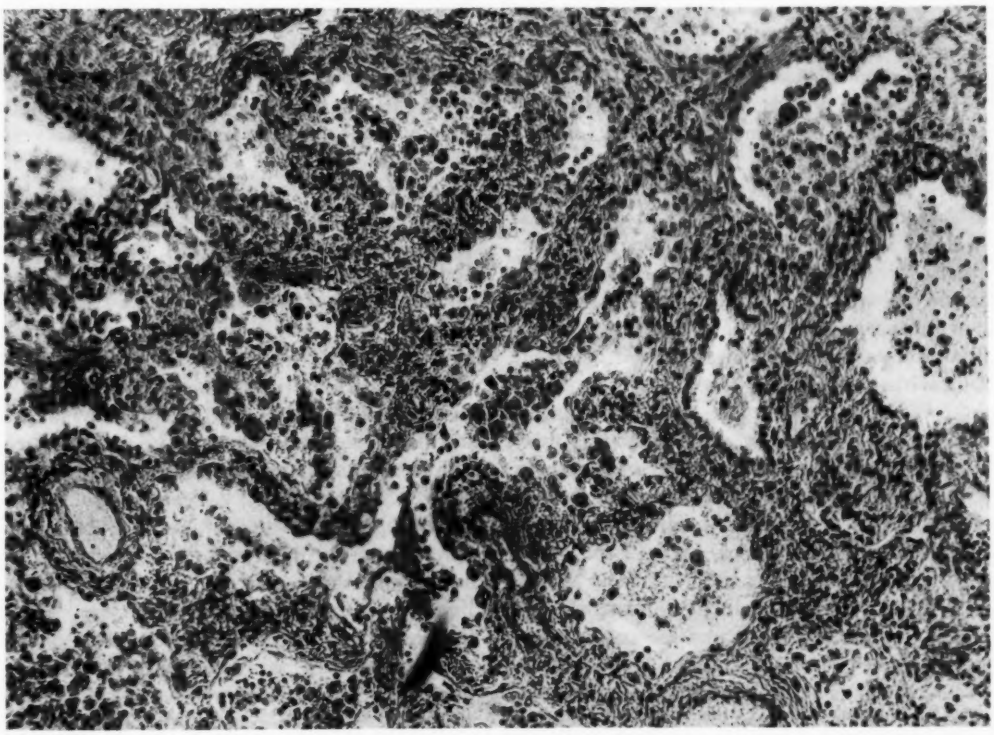

FIGURE 4. Case 2. Widened alveolar septa are infiltrated by acute and chronic inflammatory cells, and fibroblastic proliferation is extensive. Alveolar lining cells are prominent.

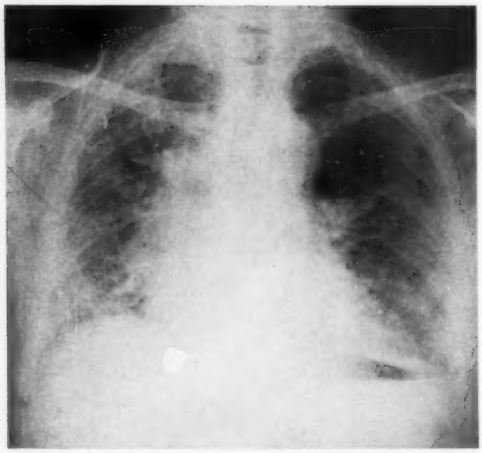

FIGURE 5. Case 3. Bilateral reticular infiltration with elevation of diaphragm was unchanged for three years.

paratracheal node did not disclose findings of diagnostic significance. Roentgenographic examination of the gastrointestinal tract revealed a small traction diverticulum in the midportion of the esophagus.

The patient was thought to have a pulmonary neoplasm or diffuse interstitial fibrosis. He was discharged on June 8, 1956, but returned July 22 because of marked progression of dyspnea, orthopnea, chest pain and blood-streaked sputum. He was afebrile. Again no edema or liver enlargement was described. He died four hours after admission.

At autopsy, evidence of a recent myocardial infarction was found. The right and left pleural cavities contained 300 cc. and 200 cc. of fluid, respectively. The lungs were of approximately twice the normal weight (800 and 1,010 gm.). The parenchyma was rubbery to palpation. The cut surfaces were gray-brown with a vague red mottling. The lower lobes were minimally edematous.

Microscopically, widened alveolar septa were heavily infiltrated by lymphocytes, with occasional macrophages and polymorphonuclear leukocytes. Fibroblastic proliferation was extensive. The alveoli contained occasional polymorphonuclear leukocytes and clusters of macrophages, some of which contained lipid. Minimal edema was present, and some alveoli contained fibrinous membranes. Bronchiolar epithelial proliferation was prominent, and in some areas an early "honeycomb" pattern was produced by irregular spaces lined by embryonal epithelium set against a background of fibrous tissue. A few fibrocalcareous tubercles were present. The bronchi exhibited chronic inflammation with hyaline thickening of the basement membranes and hypertrophy (figure 4).

This patient's disease falls in the subacute clinical category; slightly more than a year elapsed between onset and death. There was no evidence of cor pulmonale, and coronary artery disease and terminal myocardial infarction complicated the picture.

Case 3—This patient, a physician, was 61 years old when he died of diffuse interstitial pulmonary fibrosis. In 1949, seven years prior to death, he noted the onset of progressive exertional dyspnea and a chronic nonproductive cough. His annual chest x-ray that year showed "increased bronchovascular markings." He consulted a cardiologist, who reported that there was no objective abnormality except for "peculiar" inspiratory rales at both lung bases posteriorly; the rales were fine, very close to the ear, and "simulated a friction rub at times." An electrocardiogram showed left axis deviation. The patient had had severe pneumonia as a youth and two milder episodes in adult life. His history also disclosed contact with parakeets for many years. He had traveled widely but had never been ill while abroad. In 1949 he had undergone a minor surgical procedure for gynecomastia; the anesthetic agents used were PENTOTHAL®, nitrous oxide and oxygen. The pathologist's report at that time described primarily adipose tissue.

In August 1954 the patient complained of increasing shortness of breath. Physical examination demonstrated elevation and sharp limitation of motion of the diaphragm. Again the basilar rales were noted. Cyanosis of the nail beds and clubbing were also found. The heart was normal and the blood pressure was 140/90 (right arm, recumbent). Left cryptorchism was noted.

Review of serial roentgenograms of the

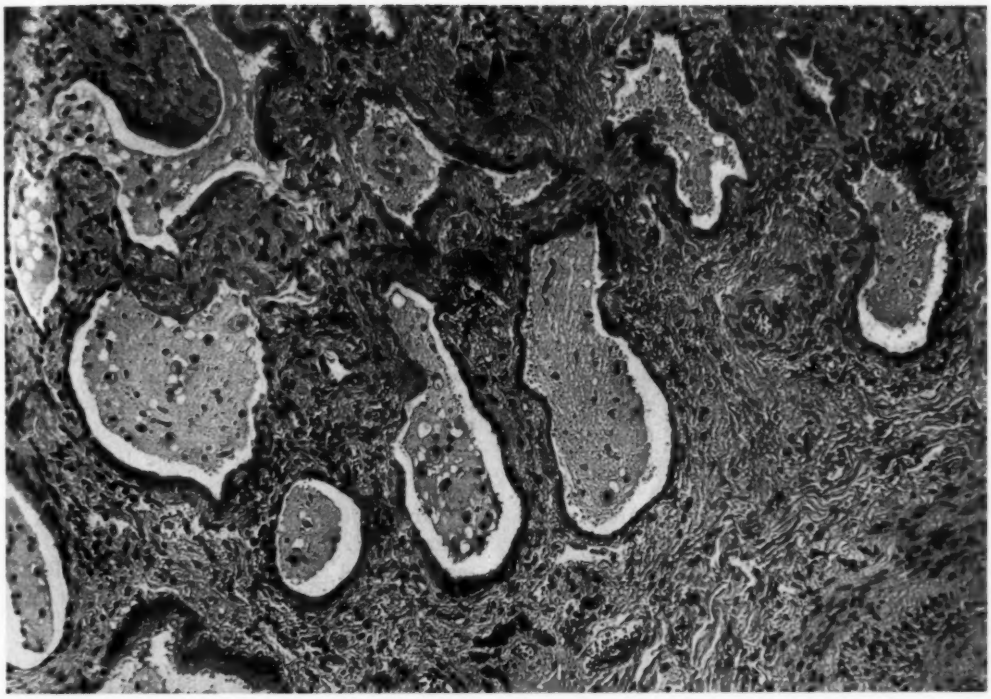

FIGURE 6. Case 3. Fibrosis is far advanced, and remaining air spaces lined by cubical to columnar epithelium produce a honeycomb pattern.

chest since 1949 showed gradually increasing bilateral parenchymal abnormality consistent with pulmonary fibrosis (figure 5). The vital capacity was 1,365 cc., and the maximum breathing capacity was 48 l. per minute. Skin tests for tuberculosis, histoplasmosis, blastomycosis and coccidioidomycosis gave negative results.

For the next year the patient took oral bronchodilators with little or no response. Reevaluation in May 1955 showed possible increase in the roentgenologic abnormality. The patient was more dyspneic although the maximum breathing capacity was 57 l. per minute.

Beginning May 18, 1955, 30 mg. of prednisolone per day was given. After six days the patient felt "wonderful," with less cough and dyspnea. The maximum breathing capacity was 95 l. per minute. The dosage of prednisolone was decreased to 20 mg. daily. One month after the start of steroid therapy the maximum breathing capacity was 108 l. per minute. The prednisolone dosage was decreased to 15 mg. per day, and the improved status was maintained for five months. In November 1955, mild peripheral edema and a marked increase in dyspnea and cough were noted. Polycythemia had developed with a hematocrit reading of 59.5 per cent. The patient had tachycardia with a presystolic gallop rhythm, and an electrocardiogram suggested cor pulmonale. He responded minimally to digitalis, diuresis and phlebotomies.

His final admission to the hospital was one month prior to death. He was so dyspneic that he was given oxygen continuously for the last month. He died seven years after the onset of dyspnea and the appearance of the abnormality on the chest x-ray.

Laboratory studies between 1954 and 1956 demonstrated the development of mild polycythemia from a hematocrit reading of 46 per

cent to a peak of 59.5 per cent. The leukocyte count ranged from 8800 to 10,100 with a normal differential pattern. Repeated examinations of sputum failed to reveal pyogens, fungi or acid-fast bacilli. *C. albicans* was cultured several times while courses of broad-spectrum antibiotics were given for suspected respiratory infections. Total serum proteins, albumin-globulin ratio and serum electrolytes remained normal. Complement fixation tests for psittacosis made on two occasions, a year apart, were positive in a dilution of 1:8.

At postmortem examination the lungs were of normal weight (390 and 380 gm.). The parenchyma was firm and finely granular. The cut surfaces appeared dry, and the cut ends of pulmonary vessels were prominent. The main pulmonary arteries were dilated and contained nonocclusive, minimally organizing mural thrombi.

Microscopically, fibrosis and bronchial epithelial proliferation were marked. A "honeycomb" pattern was produced by the many irregular spaces lined by columnar to cubical epithelium, amidst a dense fibrous stroma. Lymphocytic infiltration was mild, and occasional lipid-containing macrophages were encountered. The bronchiolar smooth muscle was hypertrophic. Pulmonary arteriosclerosis was prominent. The bronchi exhibited hyalinization of the basement membrane and hypertrophy of smooth muscle (figure 6).

This man had a prolonged course, and multiple studies to determine the cause of illness were negative except for the low complement fixation titer of 1:8 for psittacosis. Clubbing and polycythemia developed, as seems usual in the protracted forms of the disease. There was an initial good response to prednisolone. Reduction of dosage from 30 to 15 mg. per day did not result in sudden worsening, as has been described.[2]

Discussion

Of the 10 patients with pathologically proved diffuse interstitial pulmonary fibrosis, eight were men and two were women. They ranged in age from 31 to 81 years, averaging 56 years. The shortest duration of illness was four weeks, the longest seven years; the average was 27 months. In three cases the criteria for the acute form of the disease were met. Four cases were subacute, and three were classifiable as chronic, with a history in excess of two years. Seven patients demonstrated clubbing, while only two had hematocrit readings greater than 50 per cent. Leukocytosis (total leukocyte count 10,000 to 15,000) was present in seven at some time during the course and in most instances could not be related to obvious infection.

The clinical picture in these fatal cases was characterized by progressive dyspnea, chronic cough productive of variable amounts of sputum, and episodes of respiratory infection. Clubbing and polycythemia were often present. In many cases cor pulmonale developed prior to death.

The 12 patients in whom the diagnosis of diffuse interstitial pulmonary fibrosis was made but not substantiated pathologically are alive at present. Enough time has elapsed since diagnosis to classify the disease as subacute or chronic. The age and sex distribution is similar to that in the fatal cases. The average duration of signs and symptoms is five years. One patient has had clubbing and roentgenologic abnormality with minimal symptoms more than 15 years. Eleven of the 12 patients have clubbing. Five have polycythemia.

An interesting observation is that clubbing or an abnormality on the chest roentgenogram, or both, preceded other symptoms or signs in nine of 22 patients. Two patients had clubbing more than five years before there were any other findings.

The most constant physical finding in this series has been the peculiar rales, which are loud, crackling and close to the ear and resemble a series of short friction rubs. It is noteworthy that in several instances physicians described the sounds as "peculiar" or "bizarre" even before there was any emphasis on their unusual quality. It is believed that these rales are an important diagnostic aid.

The cause or causes remain obscure, but there is evidence to suggest that the Hamman-Rich syndrome is a tissue response to many agents.[3] Many etiologic possibilities have been advanced to explain diffuse interstitial fibrosis

TABLE 1

ETIOLOGIC POSSIBILITIES IN DIFFUSE INTERSTITIAL FIBROSIS

1. Unresolved viral or bacterial pneumonia
2. Mycotic infection
3. Hypersensitivity response of lung
4. Pneumoconiosis
5. Chemical pneumonia (inhalation of toxic fumes)
6. Connective tissue disease
7. Vascular disease, e.g., multiple pulmonary emboli

TABLE 2

MAJOR DIFFERENTIAL DIAGNOSES IN DIFFUSE INTERSTITIAL FIBROSIS

1. Bilateral bacterial or viral pneumonia
2. Lymphohematogenic metastases of neoplasm to lung
3. Terminal bronchiolar cell carcinoma
4. Tuberculosis
5. Sarcoidosis
6. The deep mycoses
7. Pneumoconiosis
8. Other conditions (including connective tissue disease, uremia, tuberous sclerosis and congestive heart-failure)

(table 1). It is beyond the scope of this paper to review all the theories except as they may relate to the patients in this series.

Six of the 22 patients had a history consistent with bacterial or viral pneumonia at onset.[3] Adequate bacterial and viral studies were not done, and, of course, it is possible that a respiratory infection merely brought to light the previously established disease.

Mycotic infections with histoplasmosis or organisms not currently recognized as pathogens might result in diffuse interstitial fibrosis. If any of the known mycoses are involved, one must explain the absence of specific granulomatous tissue changes. One patient, a 32 year old woman, had a positive histoplasmin skin test, and throughout the following year serial complement fixation tests for histoplasmosis were positive in titers as high as 1:32. At autopsy, granulomatous lesions were not found, and sputum as well as tissue cultures for fungi were negative. This is the only patient in the series with positive serologic tests for histoplasmosis. Two others had positive histoplasmin skin tests. Fungous cultures were negative in all cases in which such studies were made.

A relationship between diffuse interstitial fibrosis and rheumatoid disease is suggested in four cases.[3,4] A 34 year old woman had acute changes in all peripheral joints suggesting rheumatoid arthritis. Studies for rheumatic fever, lupus erythematosus and other connective tissue diseases gave negative results. She died one month after the acute onset of illness, and at autopsy the pulmonary changes of diffuse interstitial fibrosis, acute in type, were found. There was no evidence of rheumatic fever. The other three patients had less dramatic involvement of joints, but all were thought to have rheumatoid arthritis of varying severity. In none of the patients has there been associated evidence of the presence of other connective tissue disease, systemic lupus erythematosus, scleroderma, polyarteritis, or dermatomyositis.[5]

At autopsy in two cases, evidence of multiple pulmonary emboli involving small vessels was found.[3] Whether or not showers of emboli in the past resulted in fibrosis of lung parenchyma is unknown.

There was no conclusive relationship between atopic allergy and diffuse interstitial fibrosis in the series.[3] Three patients had peripheral eosinophilia of less than 10 per cent, but no subjective or objective evidence of an allergic diathesis was found. Two patients had a definite diagnosis of allergic disease; one had bronchial asthma, the other allergic rhinitis.

None of the patients had received hydralazine hydrochloride.[6] None had known contact with beryllium. Patients whose history or clinical findings suggested pneumoconiosis were not included. The possibility exists that inhaled substances not now regarded as harmful may be implicated. It is also possible that a patient may be unaware of contact with a harmful material, such as small amounts of beryllium.

It is difficult to establish a diagnosis of diffuse interstitial fibrosis without either a biopsy of the lung or a postmortem examination. Careful clinical evaluation, however, allows a presumptive diagnosis in many instances. There probably are a hundred diseases resembling diffuse interstitial fibrosis on the basis

of appearance of the chest x-ray.[7] The history and physical examination will reduce sharply the number of possibilities. Laboratory studies and time will narrow the list further. The major differential problems encountered in this series are presented in table 2.

Studies leading to a presumptive clinical diagnosis and information helpful in management are as follows.

1. History
   a. Character and duration of illness
   b. Absence of contact with hazardous inorganic substances or fumes
2. Physical examination
   a. "Characteristic" rales
   b. Clubbing
3. Skin antigens for tuberculosis and the deep mycoses
4. Complement fixation studies for the deep mycoses
5. Sputum examination
   a. Pyogens
   b. Acid-fast bacilli
   c. Fungi
   d. Malignant cells
6. Chest x-ray (bilateral, diffuse, nonspecific abnormality)
7. Bronchoscopy and, in some instances, bronchography
8. Node biopsy (prescalene or palpable nodes elsewhere)

Since the diagnosis of diffuse interstitial fibrosis is partly one of exclusion, many of the diagnostic studies are valuable when they yield negative results.

The major therapeutic weapons available for treatment of diffuse interstitial fibrosis are corticotropin and corticoids.[8] They are of no value in many cases, of slight value in some, and dramatically helpful only rarely. The practical approach to a differential diagnosis is to select those patients who might benefit from hormonal therapy and who can receive it with relative safety. Patients with benign conditions requiring no treatment and patients with infection as a primary cause or secondary factor should be excluded.

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Early Diagnosis and Prognosis in Congenital Hypothyroidism

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Congenital hypothyroidism is a preventable cause of mental retardation and in most instances can be diagnosed in the first six months of life.

The pessimism often expressed concerning the prognosis in these cases has led to an erroneous belief that early diagnosis and treatment are relatively unimportant.

To obtain the best possible results with therapy, diagnosis must be early and treatment must be adequate.

Insufficient emphasis has been placed on several early symptoms and signs which, though not specific for congenital hypothyroidism, should arouse suspicion of the condition. Laboratory determinations to confirm the diagnosis of congenital hypothyroidism are generally available.

THE earlier the diagnosis of congenital hypothyroidism is established and adequate therapy is begun, the more satisfactory is the prognosis. It is the purpose of this report to point out the criteria that should lead to this important early diagnosis. Present methods of treatment will be outlined, and comments will be made on the prognosis.

GEORGE H. LOWREY

The findings of a survey of a large number of cretins seen in recent years at The University of Michigan Medical Center emphasize the importance of early diagnosis. These patients were referred to the Center for confirmation of the diagnosis and to begin therapy. Their average age at the time of diagnosis was 12 months. Fifty-four per cent had at least three prominent symptoms of hypothyroidism by the end of the first month of life, and 75 per cent had three or more symptoms by the end of the third month.[1] If the diagnosis had been established at that time, the incidence of mental retardation would have been much lower. Eighty-two per cent of the patients in whom the diagnosis was established before the age of

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six months and who were adequately treated had an I.Q. of 80 or above, compared with 20 per cent of those whose disease was diagnosed after the age of six months and who were adequately treated (figure 1).

Early Diagnosis of Cretinism

Table 1 lists the major symptoms of a group of 49 cretins and gives the incidence for this group and for a group of 100 normal infants chosen at random from a well baby clinic.

The term "lethargy" was seldom used by parents, but this symptom complex constituted a part of the chief complaint in nearly two-thirds of the histories taken and was noted by the parents before the end of the third month of life in this number of patients. The mothers interviewed would make such statements as "She was unusually quiet and never moved much," "She almost never cried," or, as one said, "She was the best baby I ever had." It should be emphasized that the parents seldom noted retardation of motor development until several months after the initial observation of lethargy had been made.

Sluggish intestinal peristalsis as manifested by constipation was a commonly recognized characteristic of the hypothyroid patient. Only a small number of the cretins did not manifest this difficulty. The constipation was very persistent and often resisted the usual methods of treatment. One-third of the patients had some difficulty with bowel movements during the first month of life, and more than two-thirds had constipation by the third month. Typical statements by parents were "She had only two bowel movements a week and she had a hard time having those" and "The baby almost never had a bowel movement without an enema." The stools were hard and dry, and several of the mothers said their children had never had a normal bowel movement until thyroid therapy was started.

A frequent and significant finding was difficulty in feeding. This problem and failure to gain weight were the most common complaints during the first six months of life. The baby was often described as being very slow in nursing, requiring an hour or more to consume 2 or 3 oz. of formula. It was typical for the mother to relate many visits to the physician with frequent changes in formula or nursing technics but without improvement in feeding habit. Undoubtedly the lack of enthusiasm for food was related in part to the general somnolence of these infants, and as time went on a large tongue was another factor interfering with sucking and swallowing.

Noisy respiration was a frequent complaint, and several infants were described as having had "a nose cold" or "a stuffy nose" since birth. In some instances a large tongue interfered with sucking and swallowing to such an extent that it caused further respiratory difficulties and often would lead to choking. It is of interest that approximately one-third of the

TABLE 1

SYMPTOMS IN HYPOTHYROIDISM

SYMPTOM	INCIDENCE*	
	49 Cretins	*100 Normal infants*
Lethargy	96	0
Constipation	92	2
Feeding problems or failure to gain	83	5
Respiratory problems	76	6
Dry skin	76	1
Thick tongue	67	0
Hoarse voice or cry	67	0
Umbilical hernia	67	8
Prolonged icterus neonatorum	12	0
Goiter	8	0

*Expressed as percentages, indicating a positive response obtained in the history or noted by parents during the child's first six months of life. The 100 normal infants were chosen at random from the University Hospital Well Baby Clinic.

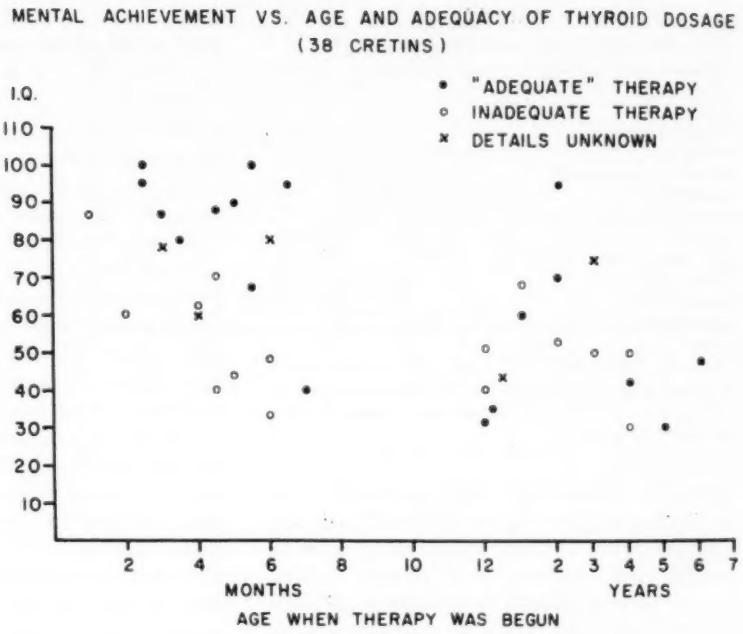

FIGURE 1. Intelligence quotients of 38 cretins. Note that when therapy was begun before the age of six months and was "adequate" (see text) the prognosis was much better than it was when treatment was begun later or when it was inadequate.

children had cyanotic attacks in the first few days or weeks of life (although it is difficult to assess a history of cyanosis during the neonatal period unless it actually is observed by the physician), and that in several instances oxygen was administered for longer than 24 hours after delivery.

One-third of the parents noted excessive dryness of the baby's skin in the first month of life, and more than three-fourths of the parents described this symptom in the fourth month. An often-repeated observation was that oils and creams gave either no relief or only temporary improvement. Other findings related to the skin were pallor, mottling and "coldness." Carotenemia ("yellow skin") was observed fairly frequently. Several mothers noted prolonged icterus neonatorum lasting longer than 10 days.

Thickening of the tongue to the point where it protruded from the mouth and interfered with feeding or respiration was observed often before the beginning of the third month and almost universally by the fifth or sixth month of life.

Umbilical hernia was present in two-thirds of the patients and was noted at the time of birth or very shortly thereafter.

All these symptoms are relatively nonspecific and conceivably could be caused by other conditions than hypothyroidism, but the presence of a combination of three or more should strongly suggest the possibility of this diagnosis. To delay diagnosis until such features of cretinism as myxedema with coarsened features, broad nose, short extremities, protuberant abdomen, short spadelike hands, and myxedematous folds over the neck and shoulders appear may result in irreparable harm to the patient's central nervous system. These features appear relatively late in the course of the disease. Similarly, it is detrimental to wait for evidence of marked retardation of motor development before entertaining the diagnosis of congenital hypothyroidism.

Some early physical findings, while not specific for cretinism, should alert the physician and may indicate the need for further diagnostic procedures. Umbilical hernia is associated with other abnormalities and occurs in a small number of normal newborn infants, but it is more common in cretins. Prolonged icterus

TABLE 2

PHYSICAL FINDINGS IN HYPOTHYROIDISM*

FINDING	PER CENT
Umbilical hernia	70
Lethargy	70
Retarded linear growth	60
Hypothermia	55
Respiratory embarrassment	50
Dry skin	50
Early myxedema	50
Bradycardia	35
Large tongue	30
Carotenemia	30
Goiter	5

*Physical examination of 20 infants with congenital hypothyroidism in whom the disease was diagnosed before the fifth month of life.

appearing one to four days postnatally and lasting more than two weeks should heighten suspicion that thyroid insufficiency may be present. The frequency of respiratory difficulties of varying degree in our group of cases deserves emphasis. This is a symptom complex which is either touched on only briefly or omitted entirely in the descriptions of cretinism in many textbooks.

Very few cretinous infants will attain the expected normal linear growth for their chronologic age. Deviation from the normal weight usually is less marked, but as time progresses the weight also deviates more and more from the expected value. Table 2 outlines the frequency of these and other physical findings among 20 infants with congenital hypothyroidism at the time of admission to our hospital; the disease was diagnosed in these cases before the fifth month of life.

The mother's prenatal history and the birth history seldom are useful aids to diagnosis. In our series the average weight of the children at birth was slightly above normal, but probably not significantly so. A family history of hypothyroidism may be significant; there were two or more cretinous siblings in 10 per cent of the families.

Laboratory Aids to Diagnosis

The most consistent laboratory finding in our patients was a protein-bound iodine (PBI) level in the blood of less than 3.4 μg. This was found at all ages, including one patient in whom the diagnosis was made at the age of five days. The determination of butanol-extractable iodine (BEI) gives similar low results in these patients. These two methods are now available in many hospitals or laboratories. Almost the only exception to these abnormally low values will be found in cretins with an inborn error of metabolism associated with an enzymatic defect and the production of abnormal iodinated proteins by the thyroid gland which, however, have little or no metabolic effect. In most such cases the patients have goiters at or soon after birth, and a family history of the condition often is present.[2]

Uptake of radioactive iodine (I^{131}) by the thyroid will be markedly depressed in most cretins. A small proportion of the patients who have a defect of synthesis associated with a goiter may have a normal or an increased uptake of radioiodine. In most patients with a genetic thyroid dysfunction, an abnormal curve will be obtained over a 24 hour period if readings are taken at intervals during that time. A relatively rare form of hypothyroidism is associated with a normal uptake of iodine by the thyroid gland but an inability to combine this iodine with the amino acids necessary for production of thyroid hormone. If these patients are given a small dose of potassium thiocyanate, the gland will be washed free of the radioiodine (figure 2). Sometimes it is necessary to use more detailed laboratory tests to determine the abnormal type of protein-bound iodine that is being formed and released by the gland. Routine use of I^{131} as a diagnostic test is not recommended due to the hazard of radiation in such young patients.

The alkaline phosphatase level in the serum was lower than normal in the majority of the patients in whom this determination was made. Other investigators have reported similar low values.[3]

The level of cholesterol in the blood was measured in 42 of our 49 patients. Among 17 patients who were less than six months of age, only three had values above the normal range of 250 mg. per cent. Determination of the cholesterol level in the first six to nine months of life is very unreliable as a diagnostic cri-

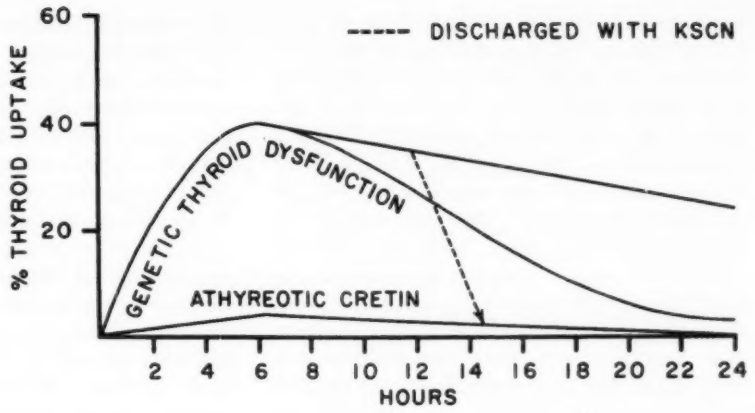

FIGURE 2. Radioiodine uptake in cretinism; types of curves for the thyroidal or neck area that may be encountered in various forms of congenital hypothyroidism. An initial normal uptake may be present in some type of genetic (enzymatic) thyroid dysfunction. Use of potassium thiocyanate to "wash out" free iodine from the gland is indicated by broken line.

terion of congenital hypothyroidism. Some degree of anemia is common but usually is not diagnostic of any thyroid dysfunction.

Radiologic examination of the bones to determine the degree of maturation is very useful as a screening technic. In the first four months of life, the distal femoral epiphysis and the foot are examined. After four months of age the wrist is the most useful area for evaluation. Without exception, the longer adequate therapy is delayed the more marked is the retardation of bone maturation. This is such a constant finding that the statement probably can be made that in the absence of retardation hypothyroidism does not exist. It should be evident that there are other causes of retardation of ossification unrelated to thyroid dysfunction. Epiphysial dysgenesis, a mottling of the epiphyses which has been described by Wilkins,[4] is pathognomonic of congenital hypothyroidism; however, it may not be present in all cases.

Therapy

One may classify patients with congenital hypothyroidism into three general categories: (1) a small group with a genetic thyroid dysfunction or an inborn error of metabolism and a synthetic defect in the formation of thyroid hormone, usually associated with goiter; (2) another small group with a vestigial thyroid gland able to produce some thyroid hormone but not an amount sufficient to maintain normal metabolism and growth of the central nervous system; and (3) the largest group, representing probably between 75 and 80 per cent of all cretins in this country, who are born without a thyroid gland. Regardless of the type, the method of treatment is essentially the same. Our plan of therapy is as follows.

As soon as the diagnosis is made, desiccated thyroid U.S.P. is given in gradually increasing amounts until laboratory and clinical evidence indicates an essentially euthyroid condition. The initial dosage is 15 mg. daily for one week. Each subsequent week the daily dose is increased by 15 mg. until a dose of approximately 120 mg. a day is being given. During this initial period of therapy the infant may actually lose weight, because of disappearance of the myxedematous subcutaneous tissue. After this initial period of therapy the features of hypothyroidism begin to disappear from the face, the child usually is more alert and active, constipation either is no longer present or it is considerably improved, the skin becomes more normal in texture, and bradycardia is partly or totally corrected. A protein-bound iodine determination is made at this time. If there has been satisfactory clinical progress and if the protein-bound iodine value is 5 μg. or more, therapy is maintained for a few months and then the dosage is increased again by 15 mg. daily and the patient's condition evaluated at approximately monthly intervals. Some of our patients have become mildly hyperthyroid with this method, but we have seen no long-term ill effects. We do not ex-

ceed a dosage level of 180 mg. daily. A number of patients less than one year of age have tolerated this dosage very satisfactorily. They have gained weight, slept well, and have not shown any "nervous" manifestations or had diarrhea or any other symptoms of toxicity. We are convinced that many of the dosage schedules which have been recommended for these patients have been inadequate and that our results support this statement. It is true that many of the patients in whom hypothyroidism is not recognized until they are past their first birthday may not tolerate such large doses, but we feel that this intolerance is due not so much to the fact that they are hyperthyroid as to the fact that they are mentally defective and that bringing the metabolic rate up to normal exaggerates this deficiency.

Prognosis

Until quite recently there has been a general feeling of pessimism concerning the prognosis of congenital hypothyroidism. This idea still pervades much of the present-day literature. It is probably this misconception that has engendered the idea that early diagnosis and treatment are of relatively minor importance. The experimental work of Eayrs and Horn[5] and the clinical reports of Smith and associates[6] and Pickering and Fisher[7] tend to disprove the bleak outlook assumed by many physicians and lay persons concerning the value of early diagnosis and adequate treatment.

It is quite possible that the thyroid gland in the fetus furnishes an important element in the normal development of the central nervous system. In the absence of this gland the maternal hormone may be insufficient or may not cross the placenta in adequate amounts to insure normal development. On the other hand, a sufficient amount of thyroid hormone does cross the placental barrier from the mother to the developing fetus so that many of the overt signs and symptoms of hypothyroidism are absent at the time of birth. A fact that makes one suspect an inadequacy of the maternal hormone is that in many newborn cretins examined roentgenologically during the first several months of life the bony development is more consistent with fetal than with neonatal chronology.[8] Similar delay probably takes place in the central nervous system. Therefore, it is quite possible that even if the administration of thyroid were started immediately after birth a small percentage of these infants would have mental retardation as a result of irreparably delayed development of the brain. The longer this deficiency exists, however, the more severe will be the retardation of mental development. If treatment is begun early, preferably before the age of six months, and if it is adequate, the prognosis for mental achievement will be at least sufficient to keep most of these children out of the mentally retarded group as defined by law in most states and as indicated by their achievement in society.

Physical development is satisfactory, as measured by standard tables of height and weight, after about two years of adequate therapy. If the diagnosis is not made until the child is more than two years of age, retardation in growth may persist. In a group of 36 institutionalized cretins in the state of Michigan, we found that the majority had subnormal stature and weight. However, the average age at which the diagnosis of cretinism was made was four years, and the average age at which treatment with desiccated thyroid was started was eight years.[9]

In a small percentage of treated patients, we found that the bone maturation actually was accelerated beyond the norm for the chronologic age, but never beyond three years. A small number of these patients have now reached adolescence, and none of them have shown precocious sexual development nor have they stopped growing prematurely.

Summary

We believe that in most circumstances congenital hypothyroidism can be diagnosed before the patient is six months old. A survey of a large group of cretins revealed that more than half had at least three prominent symptoms of congenital hypothyroidism by the end of the first month of life, and three-fourths had three or more symptoms by the end of the third month. Laboratory studies to confirm a suspicion of congenital hypothyroidism are

generally available. It is unfortunate that the pediatric literature on hypothyroidism does not place sufficient emphasis on the early appearance of the several important, although nonspecific, symptoms and signs, and that in describing the typical cretin it fails to emphasize that many of the classic physical findings are relatively late in onset. In order to obtain the best possible results with therapy, diagnosis must be early and the therapy with desiccated thyroid must be adequate. We have attempted to outline the early diagnostic criteria of congenital hypothyroidism and the proper therapy, in the hope that physicians realize this is a preventable cause of mental retardation.

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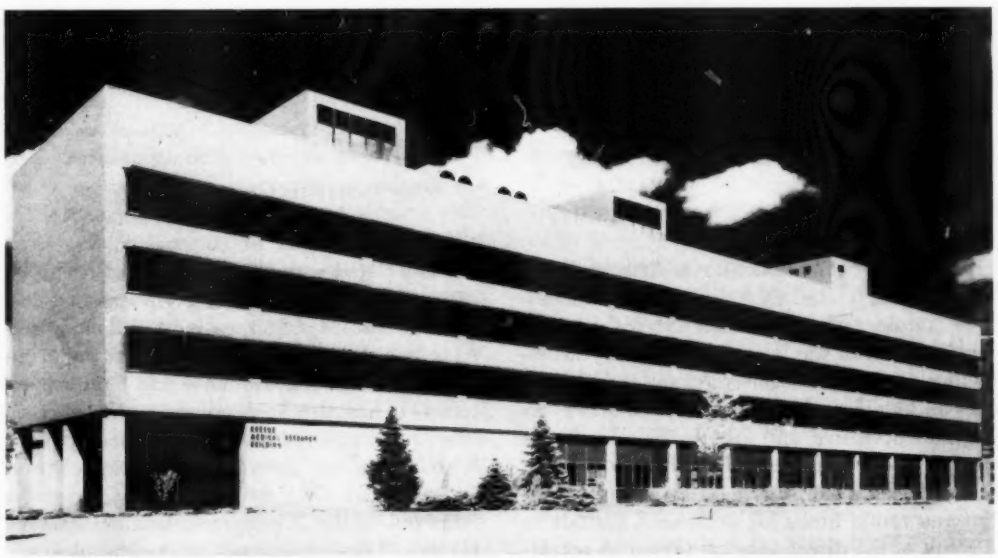

KRESGE MEDICAL RESEARCH BUILDING, UNIVERSITY OF MICHIGAN MEDICAL CENTER

Surgical Management of Arterial Peripheral Vascular Disease

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Much progress has been made in the past decade in the surgical management of arterial peripheral vascular disease. Future advances must be based on a better understanding of underlying physiologic defects so that preventive measures can be instituted before organic damage occurs in the vessels.

ONE of the exciting recent episodes in the field of surgery has been the application of direct surgical technics to diseases of the aorta and peripheral arteries. As little as 10 years ago, peripheral vascular surgery consisted mainly of operations for varicose veins and their complications and arteriovenous communications. Arterial insufficiency was treated by indirect medical measures and occasionally lumbar sympathectomy. Amputations of the leg were frequently necessitated by arterial occlusive disease. Although the underlying physiologic disturbances related to occlusive and spastic disease of the peripheral vessels are still poorly understood, many patients can now gain symptomatic relief and retain limbs for prolonged periods as a result of the direct surgical measures recently developed.

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Atherosclerosis Obliterans

The best results of surgical management are associated with the treatment of occlusive disease of the aorta and peripheral vessels. Atherosclerosis obliterans most commonly affects the abdominal aorta distal to the renal vessels and the iliac, femoral and popliteal arteries. It has also been noted in almost every other medium-sized artery in the body. Grossly the involved arteries are thickened and tortuous and have irregular or occluded lumina due to the development of atheromatous plaques. These atheromas frequently ulcerate, and when this occurs fibrin is deposited on their surfaces. As a result, thrombosis of varying degrees usually occurs concomitant with

atherosclerosis. Once thrombosis is present within a vessel, proximal propagation of the thrombi is frequent. The resultant organic changes within the lumen of the vessel impede the flow of blood, and consequently the patient's subjective symptoms and clinical findings are related to the ischemia of the tissues supplied by these vessels.

The symptoms of arterial insufficiency are largely confined to the lower extremities but depend to a great extent on the location of the most proximal obstructing lesion and on the degree of collateral circulation about this obstruction. Intermittent claudication usually occurs. At first it is unilateral, unless the abdominal aorta is involved. Later, rest pain, most marked in the digits, is noted and still later the pain and ulceration of gangrene.

Physical findings consist of diminished or absent peripheral arterial pulsations, loss of hair, atrophy of the skin and muscles, and occasionally gangrene of the skin. Decreased skin temperature of the affected extremity is also apparent. Patients usually present themselves for treatment soon after the symptoms of claudication occur and before advanced gangrene is present.

Most cases of peripheral occlusive disease can be accurately diagnosed on the basis of the patient's history and a careful physical examination. However, even though complications are associated with angiographic studies, the presence of occlusive disease still constitutes an indication for contrast-medium visualization of the outflow tracts. Unless adequate outflow tracts are present distal to the site of the known obstruction, little benefit will be derived from excision and graft replacement of an occluded arterial segment. Angiographic studies done in recent years have shown that in many instances arteriosclerotic occlusive disease of the lower extremities is segmental in nature and associated with relatively normal patent vessels both proximal and distal to the obstruction. This knowledge has in large measure been responsible for the present-day aggressiveness in the surgical management of occlusive arterial disease of the lower extremities.

The direct methods now employed in the surgical management of occlusive disease of the aorta and peripheral vessels are (1) thrombo-endarterectomy, (2) excision of the diseased segment and graft replacement and (3) bypass grafting. Each technic is of value when properly selected. The choice depends largely on the location and extent of the lesion. The basic goal of therapy is to increase the blood supply to the distal arterial tree and the tissues supplied by these vessels.

With aorto-iliac occlusions, large-caliber vessels are present which facilitate many of the technical aspects of the operative procedure. Where localized occlusive disease is confined to the distal aorta and iliac arteries, and is associated with minimal damage to the intima proximal and distal to the obstructing segment, thrombo-endarterectomy serves well to re-establish maximal blood flow. We have found that transecting the iliac arteries completely, distal to the obstruction if possible, and performing the endarterectomy in a proximal direction is a most satisfactory procedure. This has been advocated by DeBakey and associates.[1] Where the occluding segment is localized, but associated with extensive arteriosclerotic disease of the more proximal aorta and atheromatous ulceration, excision of the involved segments of aorta and iliac vessels with graft replacement is indicated.

A bifurcation bypass graft for aorto-iliac disease has seldom been used in our clinic. DeBakey and co-workers[1] believe this is the procedure of choice in situations where the occluded vascular segments are long, and in patients in whom segmental occlusion has recurred following earlier operative procedures. Since this operation produces less operative trauma and tissue injury as well as less interruption of collateral channels, they also believe it to be useful in patients of advanced age. For a bypass graft to function, adequate outflow tracts are essential. The proximal end of the graft is anastomosed to the anterior wall of the lower abdominal aorta, and the distal ends are joined to the side of the common femoral artery. Occasionally it is necessary to suture the lower end of the graft to the popliteal arteries if extensive disease is present in the superficial femoral arteries.

Much attention has been given to the type of graft employed in vascular reconstruction. The most popular grafts to date, and those with which the most experience has been obtained, are arterial homografts and synthetic prostheses. The synthetic substances used have been IVALON®, ORLON®, nylon, DACRON® and TEFLON®. The large number of arterial substitutes that have been used clearly shows that, at this time, the ideal material has not been found. Recent reports overwhelmingly favor the use of synthetic grafts over arterial homografts.[2,3] The early results with aortic homografts were exceedingly satisfactory since they are technically easier to suture than synthetic grafts. This early optimism, however, soon declined as later reports described gradual loss of elasticity, late aneurysm formation and rupture, occlusion, and failure of the graft to be replaced by the host's tissues. These complications, coupled with the difficulties of preparing and obtaining suitable homografts, have led to the extensive use of the synthetic substances. Presently, Dacron and Teflon appear to be tolerated best by the body; however, the search for the ideal replacement material is being continued. None of the synthetic prostheses have been implanted long enough to determine their ultimate fate.

The surgical correction of femoropopliteal occlusions is more difficult since the caliber of the vessels is much smaller than those more proximal. Adequately patent vessels distal to the known obstruction must be present to restore circulation to the ischemic tissues. If satisfactory outflow tracts are not present, little benefit will be derived from relieving a more proximal obstruction. Thus, in all cases of femoropopliteal occlusion, arteriographic studies should be done to visualize the smaller distal arterial tree.

The choice of operation for the femoropopliteal region depends on the angiographic findings. Early in our experience the involved segments were excised and replaced by grafts. However, a high percentage of failures in this group of patients has prompted us to employ the more conservative bypass graft method. The graft is sutured to the side of the common femoral artery proximal to the obstruction and to the side of the popliteal artery distal to the obstruction. This procedure has the advantage of not disturbing the collateral blood supply that has developed about the obstructed segment, and it is technically easier to perform since the anastomotic sites are larger than when end to end anastomoses are done.

Thrombo-endarterectomy is done when short, well-localized obstruction is present in the superficial femoral artery. The artery is completely transected distal to the obstruction and the endarterectomy carried out in a proximal direction. The vessel is then anastomosed in an end to end fashion using 5-0 or 6-0 arterial silk sutures. Precise suturing is important in these small-caliber vessels; imperfect sutures or excessive trauma to the artery may be followed by clotting and postoperative occlusion.

Lumbar sympathectomy also has a definitive place in the treatment of arterial occlusive disease of the lower extremities. It is done in patients in whom a direct arterial procedure is contraindicated by the extensiveness of the disease and in whom sympathetic nerve activity to the lower extremities is demonstrable. The sympathogalvanic reflex as described by Lewis[4] has been employed in our clinic to determine the presence of sympathetic nerve activity preoperatively, and to determine the completeness of the sympathectomy postoperatively. This test, when used in conjunction with lumbar sympathetic block, has also been useful in predicting whether or not benefit will be derived from lumbar sympathetic ganglionectomy. Lumbar sympathectomy is also of value when it is done before, or concomitant with, direct arterial procedures of the femoropopliteal vessels, particularly when the status of the outflow tracts is questionable.

DeBakey and associates[1] have reported the most extensive experience with aorto-iliac and femoropopliteal occlusions. By selecting appropriate operations for individual patients, based on the nature of the occlusion and the presence or absence of complicating local and systemic factors, they have obtained successful results in 95 per cent of 448 aorto-iliac occlusions and in 86 per cent of 336 femoropopliteal occlusions. Thus, some patients who but

a short time ago were destined to have severe physical incapacity or amputations because of arterial insufficiency due to occlusive disease may now gain full relief of symptoms.

Aneurysms

Many statistical studies have shown that in the absence of other severe complicating systemic diseases all abdominal aortic aneurysms should be operated on.[5-8] Previously, a completely satisfactory method was unavailable to deal with these lesions. Today, with synthetic grafts, blood banks and precision surgical instruments, approach to their management is more aggressive. Since most abdominal aneurysms lie below the origin of the renal vessels, the technical problems of the operation are reduced. But even when the aneurysm arises cephalad to the renal arteries the operation of choice is excision of the aneurysm and implantation of a graft.

Advanced age is not a contraindication to operation for aneurysm. Contraindications are similar to those for any other major operation. Associated severe systemic diseases involving the heart, kidneys or central nervous system may be reasons for withholding operation.

The diagnosis of abdominal aortic aneurysm is made chiefly on the basis of the clinical examination and history. The presence of an intra-abdominal pulsatile mass with lateral expansion is pathognomonic. Roentgenograms of the abdomen, particularly the lateral lumbar view, may show calcification of the wall of the aneurysm, erosion of the lumbar vertebral bodies, or both. Early in our experience, contrast-medium visualization of the aorta was obtained in patients in whom abdominal aortic aneurysms were suspected, but translumbar aortography for this purpose has now been virtually abandoned. Translumbar aortography failed to delineate the extent of most aneurysms, and operation was eventually required in all instances. Furthermore, translumbar aortography in these patients is associated with significant mortality and morbidity.[9-11]

Results of surgical excision of abdominal aortic aneurysms are steadily improving. These lesions should be excised as soon as possible after the diagnosis is made. Elective operations are associated with relatively low operative mortality rates. High mortality rates are encountered when surgical intervention is undertaken after the aneurysm has ruptured. Indeed, DeBakey[12] reported that in the last 200 excisions of aortic abdominal aneurysms by his group the operative mortality for unruptured lesions was 1.5 per cent compared with a rate of 25 per cent when the aneurysm had already ruptured. He has also demonstrated an increase in the five year survival rate from approximately 10 per cent in untreated cases to over 60 per cent in cases treated surgically.

Aneurysms of the femoral and popliteal vessels merit the same consideration as do abdominal aortic aneurysms. Without treatment the course of these lesions is progressive. If there are no other contraindications to operation, the aneurysm should be excised and arterial continuity restored by end to end anastomosis or graft.

Peripheral Arterial Emboli

Sudden occlusion of the distal arterial tree by emboli is a surgical emergency. The common etiologic disorders producing arterial embolism are rheumatic valvular heart disease, mural thrombi of the left side of the heart, and mural thrombi developing over ulcerated atheromatous plaques in the aorta. In the majority of cases, auricular fibrillation is present. Patients sustaining peripheral arterial emboli usually complain of the sudden onset of pain in the affected extremities followed by tingling, numbness, and inability to move that portion of the extremity involved. This history and the associated physical findings of hypothermia, collapsed superficial veins, loss of reflex activity and sensation, and absence or diminution of arterial pulsations establish the diagnosis. Angiographic studies are seldom required. The location of the obstructing arterial embolus can best be determined by correlating the physical findings with the absence or diminution of specific arterial pulses. Most peripheral emboli lodge at the sites of arterial bifurcations. Thus, they are commonly found at the bifurcation of the aorta, the common iliac artery, the common femoral artery and the popliteal artery. Another frequent location is

in the region of the adductor hiatus. Emboli to the upper extremity also occur and are most common in the brachial and radial vessels.

The treatment of peripheral arterial embolism is primarily surgical and consists of arteriotomy and removal of the embolus. The increasing number of successful embolectomies reported[13-15] unquestionably reflects the more aggressive surgical approach to these obstructions as well as the increased technical skills acquired by surgeons while operating on more elective conditions involving the peripheral arteries. Best results are obtained if surgical removal of the embolus is performed within 6 to 12 hours of the embolic episode. However, the success of operation is predicated not on the elapsed time but on whether or not distal propagation of thrombosis has occurred in the arterial tree. Shumacker[14] stressed that excellent results can be obtained when operation is carried out as late as 48 hours after embolism. He also has found that bypass grafting procedures are of value when patients who have viable extremities but impaired circulation are treated later.

When the diagnosis of arterial embolism is made, intravenous heparin should be given and regional sympathetic ganglion block performed. For embolism of the lower extremities, low spinal anesthesia not only blocks the sympathetic ganglia but also provides analgesia for embolectomy. Except when other systemic contraindications exist, surgical intervention is undertaken as soon as the diagnosis is established.

Thromboangiitis Obliterans

Thromboangiitis obliterans or Buerger's disease is less frequently diagnosed now because peripheral angiography has demonstrated segmental arterial occlusions in most patients in whom this diagnosis is considered. Indeed, some authors seriously question the existence of this entity and believe that it may represent only a manifestation of atherosclerosis obliterans in younger persons.[16-19] Angiographic studies are of value in localizing the obstructing lesions and delineating outflow tracts.

Treatment of Buerger's disease, regardless of its etiology, consists of restoring circulation to the distal arterial tree by the direct surgical measures previously mentioned. In addition, lumbar sympathectomy is recommended to increase collateral circulation and to prevent hydrosis, which otherwise would be present. These younger patients also are advised to abstain from the use of tobacco. Finally, instruction in foot hygiene is given. By employing these operative and nonoperative measures, the incidence of major limb amputations has decreased and the percentage of the afflicted able to retain a useful extremity after local amputation increased.

Raynaud's Disease

Raynaud's disease is a primary paroxysmal vasospastic condition involving the digital arteries or arterioles. It is most frequent in young women and involves primarily the digits of the upper extremities. The vasospasm occurs almost always in response to cold and is bilaterally symmetrical. Emotional stimuli may also precipitate an attack. Early in the course of the disease, numbness, tingling and burning of the fingers are noted in response to exposure to cold or emotional stimuli. Later, in more severe cases, pain, necrosis, ulceration or gangrene may occur. In a study from this clinic, Blain and associates[20] classified the idiopathic form of this phenomenon as Raynaud's disease only after two years had elapsed without any other underlying causative condition being detected. The term Raynaud's syndrome is used when the vasospasm is secondary to some underlying vascular or other disease. Associated diseases producing Raynaud's syndrome are arteriosclerosis obliterans, scleroderma, rheumatoid arthritis, dermatomyositis, frostbite, burns, mechanical trauma, cervical rib, scalenus anticus syndrome, and lesions of the central nervous system. In 40 per cent of the cases of Raynaud's disease studied by Blain and co-workers, the lower extremities were also involved.

Buchanan and co-workers[21] have shown that persons with Raynaud's phenomenon of the fingers and toes manifest a greater sensitivity to cold than do normal persons. This sensitivity may persist after sympathectomy and would explain why vasospastic response can

be demonstrated in some patients when they are cooled even after complete sympathetic ganglionectomy.

Since 75 per cent of the cases of Raynaud's disease run a benign, chronic course,[20] medical management is usually employed. Patients are instructed to protect the extremities from cold and injuries. Vasodilator drugs have also proved of benefit, particularly in the milder cases. When Raynaud's phenomenon is present, treatment of the underlying disease is also necessary. Finally, in those patients in whom the condition becomes progressive and is associated with pain, ulceration, necrosis or gangrene, sympathectomy is necessary. Recently we have been employing the anterior transthoracic transpleural approach suggested by Palumbo[22] when upper thoracic sympathectomy has been required. This method has the advantage of avoiding Horner's syndrome, yet provides excellent sympathetic denervation of the head, neck, shoulder and upper extremity.

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Postgraduate Training in Occupational Medicine at The University of Michigan Medical Center

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Almost every physician devotes some professional time and attention to industrially connected conditions. The University of Michigan Medical Center has developed a comprehensive postgraduate training program in occupational medicine which includes seminars, conferences and short postgraduate courses as well as graduate courses for qualification for examination by the American Board of Preventive Medicine. Both for specialty training in occupational medicine and for the educational needs of part-time industrial physicians, the facilities of a large medical center are a great advantage, and the program at the University of Michigan utilizes the knowledge and skills of many different components of the Medical Center and of other schools and departments.

FREDERICK H. SHILLITO

DIVERSE and extensive opportunities for postgraduate study in occupational medicine exist at The University of Michigan Medical Center in Ann Arbor. New courses and new physical facilities have been developed rapidly in the past few years, reflecting the increasing importance of the subject. One of the most significant developments has been the recent recognition of occupational medicine as a specialty, with certification established under the American Board of Preventive Medicine. The expanding complexities of industrial life, however, still constitute the real reasons for the increased demand for industrial physicians. While not all physicians are fitted or willing to devote themselves exclusively to the field of occupational medicine, almost every physician devotes an appreciable part of his professional attention and time to industrially connected conditions. So it is evident that a variety of courses different in length, content and purpose should be offered at the postgraduate level, enabling physicians to select the training and instruction in industrial health suited to their individual needs.

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As the practice of occupational medicine requires skill and knowledge in many fields, training at the University of Michigan is not restricted to one particular school or college but is done throughout the entire Medical Center. Integration is directed and guided by the staff of the Institute of Industrial Health, which itself is located in the Medical Center. Thus it is feasible to draw on the facilities of the School of Public Health, the Medical School, University Hospital, and other components of the Center. Further, it is practicable to secure participation from other campus schools and departments such as Engineering and Graduate Studies.

Development of the Program in Occupational Medicine

The beginnings of consciousness toward industrial diseases in the state of Michigan seem to have taken form and expression from the hand and mind of Charles H. Brigham, a pastor of Ann Arbor and a member of the state's first board of health. The year was 1875. A few excerpts from his report to the board reveal some of the attitudes of both employees and employers; though understandable, these attitudes reflect the general lack of discernment of industrial health hazards in those times.

"Individual men and women are rarely willing to allow that the calling which they have chosen is the cause of the disease which they may happen to have; and employers will insist that the health of their workmen is good, however dangerous their occupation may seem to be. The owner of a gunpowder mill will bring facts to show that his workmen are safer in their place than the laborers on a farm, and in proportion to their number fewer die violent death.

"The white lead manufacturer has figures to prove that his workmen are likely to live to a good old age. Interest and prejudice unite to underrate the risk and the disaster in one or another kind of labor. Circulars to factory owners about the health of their operatives, will bring back a very vague and uncertain report, if they get any answer to all; and questions on the spot are often treated as intrusive and meddlesome. There is no charge to which men are more sensitive, than even an implication, that in their work they are injuring their own health."

Next should be noted the career of Dr. Victor C. Vaughan which extended from 1876 to 1921 when he retired as dean of the Medical School of the University of Michigan. As a physiologic chemist, a hygienist and a toxicologist, he did much to promote an understanding of poisons, both endogenous and exogenous. He was in demand in the courtroom as an expert witness in homicide cases as well as in civil litigations pertaining to toxicology.

Instruction in industrial medicine as such was presented by Dr. Vaughan in lectures to medical students. His accounts and descriptions of personal toxicologic investigations served as an inspiration to students. Such was the earliest teaching of what later became occupational medicine as it is known today.

Another early teacher in the field was Dr. Emory Sink. He came to the University of Michigan as an ophthalmologist and practiced as such in the University Health Service, but, as an avocation, he gave lectures in industrial health to the medical students. By 1931 he had developed a course outline manual. The evolution and development of the present-day instruction in occupational medicine at the Medical Center began at that time.

In 1941, with the founding of the School of Public Health, industrial health was recognized formally and academically and Dr. Sink was appointed Assistant Professor in Industrial Health. The faculty included several notable nonresident lecturers: William G. Fredrick, Bureau of Industrial Hygiene, Detroit Department of Health; Carey P. McCord, Medical Advisor, Chrysler Corporation, Detroit; Kenneth F. Markuson, Director, Bureau of Industrial Hygiene, Michigan Department of Health; Clarence Selby, Medical Director, General Motors Corporation, Detroit.

The latest era of development of an occupational medical program at the Medical Center started in 1948 when Dr. Selby, having retired from the medical directorship of General Motors, joined the staff of the School of Public Health in Ann Arbor. Most conspicuous of the

immediate accomplishments was the creation of the Institute of Industrial Health, which has catalyzed and implemented the rapid developments in industrial health training at the Medical Center since 1951. Dr. O. Tod Mallery was the Institute's director until 1956 when he resigned to devote himself to an industrial medical directorship in the field of insurance. Dr. Seward E. Miller succeeded him. In 1958 the University of Michigan created the Department of Industrial Health in the School of Public Health, with Dr. Miller as the chairman.

Continuing Courses

There is a broad spectrum of demand for instruction in preventive medicine and hygiene as it pertains to industry. Engineers, hygienists, nurses and insurance experts as well as physicians need opportunities for precise instruction in particular phases of the subject. All these specialists serve on the industrial health team. For such persons the short seminar type of conference, lasting about three days, is an ideal instrument. In the School of Public Health such conferences are scheduled and programmed as a demand becomes evident. At these conferences the common interest in the subject matter draws all members of the health team into instructive discussion.

Some of the conferences which have been of interest to industrial physicians are the following.

1. Industrial Nursing
2. Industrial Health Environment
3. Air Pollution
4. Health in Foundries
5. Expert and Technical Testimony in Court
6. Instrumentation in Industrial Hygiene
7. Radioactive Wastes
8. Light and Vision
9. Causes of Accidents

In addition to these conferences, continuing course sessions are given which are limited to full-time industrial physicians. These annual meetings, lasting two days, have come to be known as the Selby Discussionals and have attained such an enviable status that attendance has to be limited.

Postgraduate Courses

In addition to the need for continuing education courses for those working in the field, there is a demand for short intensive courses for practicing physicians. To meet this demand the Department of Postgraduate Medicine of the Medical School and the Institute of Industrial Health are planning a short intensive course of instruction in industrial medicine. Participation is planned from the faculties in internal medicine, radiology, surgery, otology, physical medicine, and others. The course will cover poisoning, both environmental (industrial) and household (to some extent). Additional material to aid the part-time industrial physician will round out the course.

As mentioned previously, only a relatively few physicians will become fully qualified specialists in occupational medicine and devote full time to this work. Over 90 per cent of general practitioners, however, devote some time to occupational conditions. In fact, these physicians, rather than specialists, actually care for the majority of persons with industrially connected disabilities. With the trend toward decentralization of industry and with branch plants being located in smaller communities, the general practitioner is having increasing opportunities to practice industrial medicine. More physicians are serving as part-time plant physicians and are in charge of small industrial medical units. Further, the hazards of farming bring injuries which are entirely occupational in nature. The need for such short postgraduate courses is manifest.

Graduate Courses

The American Board of Preventive Medicine examines candidates for specialty certification in three subspecialties, one of which is occupational medicine. Requirements for admission to the examinations, beyond a medical degree and internship, include two years of full-time academic training in occupational medicine, toxicology and industrial hygiene; a residency of one year in an approved medical department of an industry, and at least three years of practice limited to occupational medicine.

TABLE 1

RÉSUMÉ OF ACADEMIC CURRICULUM OF RESIDENCY TRAINING IN OCCUPATIONAL HEALTH

FIRST YEAR

First semester
Required:
Principles and Methods of Epidemiology
Statistical Methods in Public Health
Public Health Administration and Law
Principles of Radiological Health
Applied Physiology in Work Environment
Industrial Hygiene
Occupational Health Seminar

Elective:
Radiological Health Seminar

Second semester
Required:
Radiation Biology
Industrial Accident Prevention
Occupational Health Seminar
Industrial Hygiene Control
Industrial Hygiene Sampling and Analysis
Compensation and Forensic Medicine

Electives:
Radiological Health Seminar
Clinical Epidemiology
Advanced Statistical Methods in Public Health
Health and Human Behavior
Relation of Chemicals to Enzyme Activity
Principles of Community Air Pollution
Industrial Health Problems

SUMMER SCHOOL

Elective:
Industrial Medical Practice (Field Work) (two weeks in university, two months in a plant)

SECOND YEAR

First semester
Required:
Clinical Medicine
Industrial Toxicology and Occupational Diseases
Research in Industrial Health (Laboratory or Clinical)
Environment and Health
Medical Care Administration
Advanced Occupational Health Seminar

Electives:
Radiological Health Seminar
Research in Environmental Health (Radiological)
Chemical Detoxication and Metabolism
Personnel Administration
Human Nutrition
Survey Research in Public Health

Second semester
Required:
Clinical Medicine
Research in Industrial Health (Laboratory or Clinical)
Advanced Medical Care Administration
Principles of Mental Health
Advanced Occupational Health Seminar

Electives:
Radiological Health Seminar
Research in Environmental Health (Radiological)
Physiochemical Structure and Pharmacologic Action
Industrial Sociology
Epidemiology of Chronic Diseases
Principles of Organization
Parasitic Diseases

At the Medical Center of the University of Michigan, adequate facilities are available for the full two years of academic training in occupational medicine. Students taking this academic training may earn the degree of Master of Public Health (Industrial Health). The student receives thorough training in basic preventive medicine courses such as epidemiology, biostatistics and public health administration. Mastery of these subjects is necessary for the first day of the Board examinations. The second day of the examination is confined to occupational medicine.

Along with the basic preventive medicine courses, the physician qualifying himself for Board certification in occupational medicine is required to take specialized courses in this field. During the first year, instruction is given in the subjects of environmental physiology, industrial hygiene and health, radiation biology, industrial hygiene control, and accident prevention. For the specialist in the field of occupational health these subjects are essential. Electives are allowed progressively through the two academic years so that the student can acquaint himself more fully with specialized areas.

In connection with these graduate years it is feasible to train physicians not only for careers in teaching and research but also for equally important careers as industrial medical clinicians. In training for this latter field, the facilities of a large medical center are of great advantage. The physicians are given training in the clinics and wards of University Hospital. In the second year fully half of the time can be devoted to clinical subjects. In addition, during the summer practical in-plant instruction in industrial medical departments

is afforded. Thus it is felt that in these graduate years a solid groundwork of training in clinical industrial medicine is achieved.

The in-plant residency year, directly supervised by the faculty, is reserved for physicians planning to qualify for certification by the American Board of Preventive Medicine. During this residency year which follows the two years of academic work the physician rotates through various plant medical departments and clinics, actively participating in all facets of the clinical work.

A résumé of the academic curriculum of residency training in occupational health is given in table 1.

Summary

From early beginnings when an occasional lecture to medical students constituted the entire curriculum, The University of Michigan Medical Center has developed a comprehensive postgraduate teaching program covering all phases of industrial health. Whether the student physician is interested ultimately in teaching, research or clinical practice, he benefits from instruction by the faculties of several schools and departments. In the full two year academic course, designed as part of the residency program to qualify physicians for examination and certification by the American Board of Preventive Medicine, the first year is largely at the School of Public Health while much of the second year is at University Hospital. The practice of occupational medicine requires skill and knowledge in many fields. Thus a large medical center is ideal for this training. Integration of the many resources has been accomplished through the Institute of Industrial Health, which has functioned since 1951. The staff members of the Institute, through academic appointments, participate actively in the teaching and provide guidance in administrative phases of the program.

While relatively few physicians restrict themselves solely to the practice of occupational medicine, almost all doctors devote some professional time and attention to industrially connected disabilities. Seminars, conferences and short postgraduate courses are designed to serve the education needs of such physicians. Here again the advantages of the proximity of the School of Public Health, the departments of internal medicine, radiology, otology, dermatology, physical medicine, and others of the Medical School are self-evident. Thus a full, complete curriculum in industrial health has been effected by drawing generously on the knowledge and skills of many different specialists in many areas of the Medical Center of the University of Michigan.

MEETINGS *and Postgraduate Courses*

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO: The sixth annual series of lectures on "The growth of medicine":

They were also patients: George Gershwin, Clarence Darrow and Adolf Hitler, February 2
The medical revolution, February 9
The history of vascular surgery, February 16
Medical illustrations, February 23
The Chamberlens and the obstetric forceps, March 1
Chest pain, through the ages, March 8

For further information, write to: Office of Information Services, Northwestern University News Service, Evanston, Ill.

UNIVERSITY OF KANSAS SCHOOL OF MEDICINE: The 1960 sessions of the Kansas Circuit Course, to be offered in eight towns, include the following postgraduate symposia: Mother and child, Postoperative diagnostic problems, Diseases of the heart and great vessels, Grandpeople medicine, Special problems, and Trends in treatment. For further information, write to: Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 12.

UNIVERSITY OF OKLAHOMA MEDICAL CENTER, OKLAHOMA CITY: Postgraduate courses for 1960:

Basic electrocardiography, February 29-March 5
Ophthalmology-otolaryngology symposium, March 3-4
Obstetric-gynecologic symposium, March 5
Third Oklahoma colloquy on advances in medicine: Physiologic and biochemical aspects of adrenal steroids, March 24-26
Carcinoma of the skin, April 22-23
Pediatric neurology, May 12-13
Orthopedic symposium, May 13-14
The Oklahoma Association of House Staff Physicians, May 6

For further information, write to: Office of Postgraduate Education, University of Oklahoma Medical Center, 800 N.E. 13th Street, Oklahoma City.

Acute Surgical Abdomen in Childhood

C. THOMAS FLOTTE AND EARL F. WOLFMAN, JR.*

University of Michigan Medical School, Ann Arbor

In the first few weeks of life, omphalocele, gastrointestinal atresia and stenosis, diaphragmatic hernia, malrotation, meconium ileus and imperforate anus are common causes of acute surgical abdomen. Hypertrophic pyloric stenosis usually is not manifested until the child is a few weeks old. Intussusception and strangulated inguinal hernia are seen most often in children less than two years old. In childhood, conditions producing acute surgical abdomen include appendicitis, Meckel's diverticulum, intestinal obstruction, and traumatic injury.

C. THOMAS FLOTTE

DIAGNOSIS of the acute surgical abdomen in children is difficult. Children usually are unable to give a subjective history, and information obtained from the parents often is colored by emotion. A child's reaction to a disease process may differ from that of an adult. For example, vomiting occurs more readily in children, and their reaction to pain is variable. Some children wince, others whimper or cry; still others lie quietly in bed. They often have diarrhea with a condition which in an adult is associated with constipation. High fever is common apart from acute infections. Localized tenderness and rigidity are often absent.

Examination of a child requires gentleness and cannot be hurried. Inspection is valuable, for a feeble cry, pallor, loose skin and parched lips with green vomitus indicate a serious illness. Abnormal peristalsis and bowel distention are easily observed through the thin abdominal wall of an infant. The hand palpating the abdomen should be warm, and the affected area approached last. Gentle palpation gives information that is completely lost to the heavy-handed.

Urinalysis, blood count and tests which reveal physiologic status should be performed, but there should be no delay in establishing the diagnosis of the acute abdomen while wait-

*Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan.

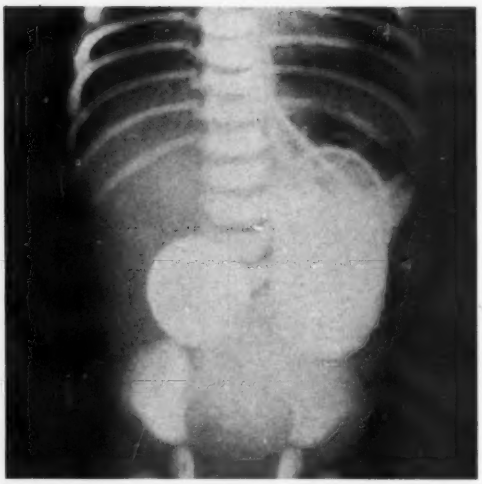

FIGURE 1. Roentgenogram using radiopaque material demonstrating the dilated stomach and duodenum in duodenal atresia.

ing for multiple laboratory determinations. Urinalysis, in addition to including or excluding urinary tract disease, may give some information on hydration. The leukocyte count, although helpful, is not as reliable a diagnostic guide in the acute abdomen of childhood as it is in adults.

Abdominal roentgenograms assist in establishing the diagnosis of intestinal obstruction. The scout or flat film usually gives the desired information. By using the newer water-soluble radiopaque materials instead of barium one can obtain contrast films showing the exact site of obstruction.

A precise diagnosis is not always possible in children. When the existence of an acute surgical abdomen is strongly suspected, exploratory laparotomy is indicated without delay.

The lesions that produce an acute surgical abdomen are not easily categorized. In newborn infants and during the first few weeks of life, developmental defects such as omphalocele, atresia and stenosis of the gastrointestinal tract, diaphragmatic hernia, malrotation, meconium ileus and imperforate anus are the common causes. Congenital hypertrophic pyloric stenosis usually does not manifest itself until the child is a few weeks old. Intestinal obstruction secondary to intussusception and strangulated inguinal hernia is seen most often in children less than two years old. Conditions which produce acute surgical abdomen and occur throughout childhood include acute appendicitis, complications of Meckel's diverticulum, intestinal obstruction from various causes, and trauma.

The Newborn Infant

Omphalocele—Omphalocele or umbilical eventration is a defect of the abdominal wall with herniation of abdominal contents into the base of the umbilical cord. It is covered only by peritoneum and amniotic sac. Urgent repair is indicated because the sac may rupture and peritonitis result. Small omphaloceles are repaired as a primary procedure. Unfortunately, many are large and it is technically impossible to reduce them into the underdeveloped abdominal cavity and still close the abdominal wall in layers. In these cases it is preferable to mobilize skin flaps to cover the herniation and repair the muscular and fascial layers later, when the abdominal cavity has enlarged.

Atresia and stenosis of the gastrointestinal tract—Atresia is a developmental defect in which a portion of the gastrointestinal tract fails to canalize. In stenosis, partial canalization has occurred so that the lumen is constricted. A child with atresia has complete intestinal obstruction. The bowel proximal to the obstruction is dilated, and vomiting is noted on the first day of life. Atresia rarely occurs proximal to the papilla of Vater, and thus the vomitus usually is bile-stained. The degree of abdominal distention depends on the level of the atresia. In duodenal atresia the distention usually is limited to the epigastrium, or it may be absent if the stomach has remained empty because of vomiting. When the atresia is more distal, distention is more marked and progressive. Roentgenograms show the dilated bowel of intestinal obstruction. Duodenal atresia can be suspected if the roentgenograms show marked dilatation of the duodenum (figure 1). In stenosis, since intestinal obstruction is incomplete, symptoms appear later in life and are less severe.

Treatment of both atresia and stenosis is

surgical. Preoperative nasogastric suction and parenteral administration of fluids to correct dehydration are necessary. The surgical technic varies with the site of obstruction, but a short-circuiting operation to bypass the obstruction is preferred. In atresia of the duodenum, duodenojejunostomy is preferable to gastroenterostomy. Since atresia or stenosis may be multiple, all of the bowel must be examined.

Meconium ileus—Intestinal obstruction from impacted meconium presents a therapeutic problem in the newborn infant. It is a generalized disease associated with decreased to absent pancreatic exocrine activity. Meconium in the bowel becomes exceedingly sticky and puttylike because of pancreatic enzyme insufficiency. Inspissated meconium usually causes mechanical obstruction in the distal ileum with distention of the proximal bowel.

Meconium ileus should be suspected at birth if the amniotic fluid is discolored or fetid, or if the abdomen is distended. Roentgenograms usually show dilated loops of bowel and a mottled or granular appearance in areas of concentration of the inspissated meconium (figure 2). Occasionally, flecks of calcium are seen throughout the abdomen, indicating a peritonitis of fetal life.

A completely satisfactory method is not available for the treatment of meconium ileus. A knowledge of its etiology coupled with the availability of pancreatic extract has increased the survival rate. Presently, the Mikulicz resection and double ileostomy or ileostomy with end to side anastomosis of the proximal ileum seem to be the most effective. In both these operative procedures, pancreatic extract should be introduced into the ileum at the site of meconium obstruction.

Diaphragmatic hernia—Diaphragmatic hernia is not an abdominal lesion, but the hernial contents originate in the abdomen and surgical repair is best done through the abdomen and it is therefore considered among conditions causing acute surgical abdomen. In childhood, it usually is due to a congenital diaphragmatic defect. There are three recognized types, namely, posterolateral (foramen of Bochdalek), hiatal and retrosternal (foramen of Morgagni).

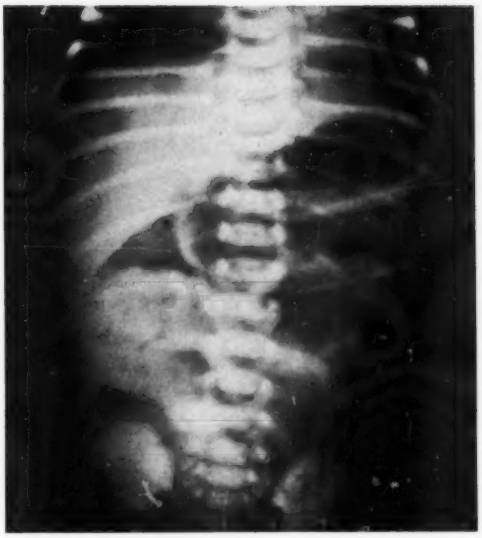

FIGURE 2. Roentgenogram showing dilated loops of bowel and the mottled appearance typical of meconium ileus.

Symptoms of dyspnea and cyanosis are noted shortly after birth. The affected side of the chest may not move, and there may be a mediastinal shift to the normal side. Auscultation demonstrates distant or absent breath sounds, but peristaltic sounds are heard clearly. Roentgenograms of the chest and abdomen establish the diagnosis (figure 3).

Early recognition and repair of the hernia are essential. The operation is best done through an abdominal incision. The abdominal viscera are removed from the chest and the defect in the diaphragm is repaired. At times when the abdominal contents have lost the right of domicile within the abdomen it is necessary to leave a defect in the fascia and close the skin; later repair is similar to that of a large omphalocele.

Malrotation of the intestine—This anomaly occurs because the embryonic midgut, which develops into the terminal ileum, cecum and ascending and midtransverse colon, fails to complete its normal counterclockwise rotation after it returns into the peritoneal cavity during the tenth week of intra-uterine life. As a result, the cecum remains in the right upper quadrant. Bands of reflected peritoneum from

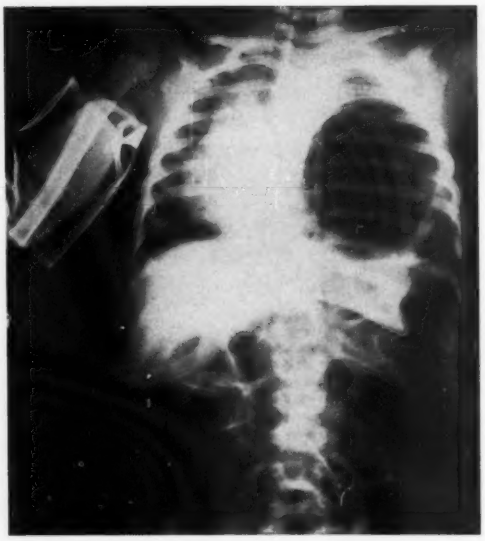

FIGURE 3. Congenital diaphragmatic hernia. Most of the stomach, part of the ileum and the transverse colon are in the left side of the chest.

the cecum may cross the duodenum and obstruct it. Further, the attachment of the small bowel mesentery to the posterior abdominal wall is short and rudimentary. Because of this short mesentery and lack of fixation of the right and left colon to the posterior abdominal wall, volvulus of the entire midgut may occur.

When obstruction of the duodenum is present, symptoms and signs are similar to those in duodenal atresia. The vomitus is bile-stained, the upper abdomen is distended, and roentgenograms show dilation of the stomach and duodenum. When volvulus occurs, the characteristic findings are pain, vomiting, toxemia and abdominal distention.

Duodenal obstruction requires laparotomy and incision of the peritoneal folds that compress the duodenum. If volvulus is present the bowel must be derotated. If it is nonviable, resection must be performed.

Imperforate anus—Congenital anomalies of the anus and rectum may present a type of gastrointestinal atresia but are usually considered as separate entities. Imperforate anus may be of several types, varying from a membranous diaphragm to complete absence of anus and rectum. Diagnosis is made by inspection at the time of birth or when the child fails to pass meconium. If the condition is unrecognized, several days may elapse before the distention and vomiting of intestinal obstruction occur.

Roentgenograms should be made with the child inverted and with a metallic marker on the anal dimple. The gas shadow in the colon and rectum indicates the extent of occlusion.

The method of surgical correction employed depends on the abnormality. If the lesion is membranous, incision followed by dilation is satisfactory. When the defect is 2 cm. or less from the skin surface, a perineal approach to the blind rectal segment with suture of the withdrawn pouch to the anal skin can be done. If the defect is more than 2 cm. from the skin surface or if there is a fistula to the vagina in the female or to the urinary tract in the male, a combined abdominoperineal approach can be used. However, under these circumstances many surgeons prefer a temporary transverse colostomy, delaying definitive repair until the child weighs 15 to 25 lb. Fortunately, infants with imperforate anus seldom have deficiency of the sphincter or nerve mechanism. Injudicious operations which damage the sphincter can result in an anal cripple.

Congenital hypertrophic pyloric stenosis—Hypertrophic pyloric stenosis (figure 4) is the most common abdominal emergency encountered in the neonatal period. The reason for the hypertrophy of the pyloric musculature is not known, and recent data suggest that it may not be congenital.

Pyloric stenosis is commonly encountered in a first-born male child, usually between the third and sixth weeks of life. Progressive vomiting without bile staining is associated with dehydration and reduction in fecal residue. Peristaltic waves are often observed passing across the abdomen from left to right, especially after feeding. A small tumor, the so-called olive, usually can be palpated in the right upper quadrant near the midline.

The Ramstedt operation with separation of the hypertrophied pyloric muscle down to the submucosa is the procedure of choice. Care must be taken when the pyloric mass is incised

to avoid entering the duodenum, because the duodenum extends up over the pyloric sphincter much as the vagina extends over the cervix. Results of surgical treatment of hypertrophic pyloric stenosis are uniformly good.

First Year of Life

Intussusception—Intussusception is a common form of intestinal obstruction seen in the first year or two of life. It occurs when one portion of the bowel telescopes into another more distal segment. Usually there is no apparent reason for the intussusception, except that occasionally a Meckel diverticulum, a polyp or hypertrophied lymph nodes may be found at the starting point.

A typical history would be that a male child less than two years old suddenly screams with abdominal pain, vomits and becomes pale and limp. The discomfort is paroxysmal and he continues to have similar episodes at 15 to 20 minute intervals. Rectal bleeding, presenting the classic "currant jelly stool," is common. Palpation of the abdomen may reveal a sausage-shaped mass in the region of the colon. In far-advanced cases the intussusception may be palpated rectally.

Barium enema has been used in an attempt to reduce intussusception. In selected early cases this may be valuable, but where the symptoms have been prolonged or the intussusception is only questionably reduced, operative therapy is mandatory.

The surgical procedure depends on the status of the bowel. Simple reduction by taxis is the ideal method. If reduction cannot be accomplished by this means or if there is a question of viability, resection should be done. Operations that are designed to prevent recurrence are of little value; the condition recurs in less than 2 per cent of treated cases.

Inguinal hernia—Inguinal hernias are common in children. Now, most physicians recommend repair in the first year of life, thereby reducing the incidence of strangulation. When a hernia cannot be reduced readily, operative

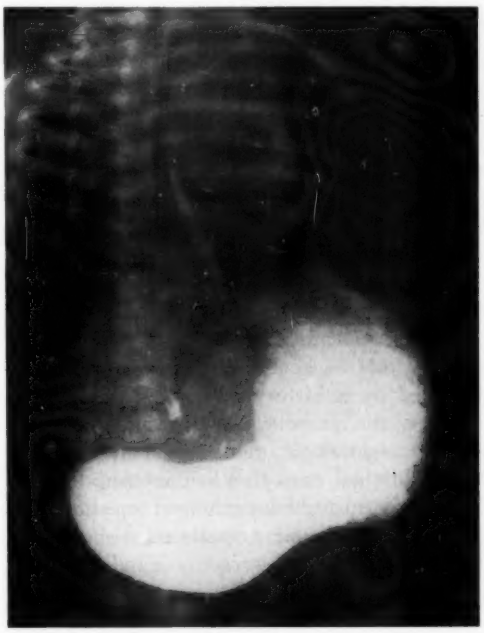

FIGURE 4. Roentgenogram showing the dilated stomach in hypertrophic pyloric stenosis.

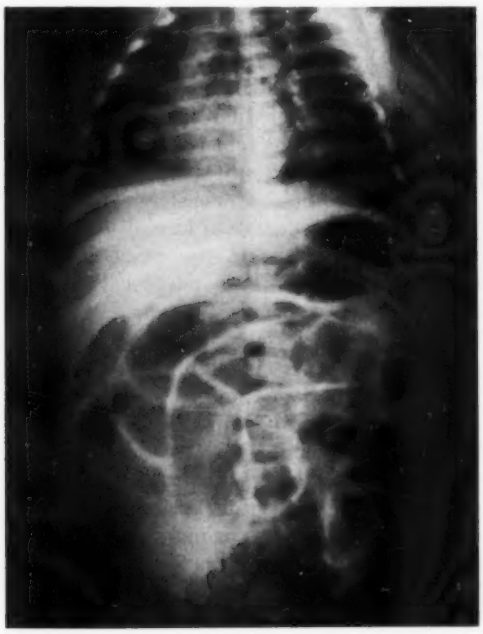

FIGURE 5. Obstruction of the small intestine secondary to an adhesive band adjacent to Meckel's diverticulum.

reduction and repair with careful examination of the involved bowel are necessary. Herniorrhaphy in a small child is easily accomplished. Plastic procedures involving the inguinal canal usually are not indicated because fascial defects seldom are present. Caution should be exercised to avoid injuring the testicle.

Childhood

Acute appendicitis—Much has been written about acute appendicitis in childhood. It is the most common abdominal surgical emergency in children. Even the most experienced observers at times find the diagnosis difficult.

The triad of abdominal pain, vomiting and fever in a young child must be regarded as indicative of appendicitis until proved otherwise. Pain is often difficult to assess, but most children indicate the presence of abdominal pain by their behavior. A child usually indicates abdominal pain by pointing to the umbilicus. Vomiting is almost always present, and frequently precedes pain. Fever as high as 104° F. may occur. Diarrhea as a symptom of acute appendicitis is more common in children than in adults.

Children with acute appendicitis tend to adopt a characteristic attitude. They usually lie on their back with the knees drawn onto the abdomen or curled on their side. Abdominal breathing may be replaced by thoracic respiration, indicating splinting of abdominal muscles. Tenderness is a constant sign and the most important evidence of local disease. Muscle guarding is frequent. Spasm of the psoas muscle may be present in retrocecal appendicitis. Peristalsis usually is normal or hypoactive. The leukocyte count may range from 8000 to 35,000 per cubic millimeter.

Differential diagnosis involves many diseases which cause abdominal pain. Acute mesenteric lymphadenitis most closely simulates appendicitis, but others are acute gastroenteritis, urinary tract infection, basilar pneumonia, exanthematous disease, primary peritonitis associated with nephrosis, acute hepatitis. Henoch's purpura, sickle cell anemia, and some spider bites.

Acute appendicitis requires appendectomy. If the diagnosis is doubtful, laparotomy should be done. It is better to operate and find mesenteric lymphadenitis than to permit acute appendicitis to progress to rupture.

Meckel's diverticulum—Meckel's diverticulum is a persistence of that portion of the vitelline duct which in embryonic life opens into the ileum. Clinically, Meckel's diverticulum resembles acute appendicitis, but the diagnosis usually is established at the time of operation. Hemorrhage may occur if aberrant gastric or pancreatic mucosa in the diverticulum becomes ulcerated. Meckel's diverticulum may also be the leading point in an intussusception, as well as a focal point for volvulus. Occasionally, adhesions form between a Meckel diverticulum and adjacent bowel, resulting in intestinal obstruction (figure 5).

Excision is the preferred treatment for complications of Meckel's diverticulum. When operation is performed in a case in which acute appendicitis is suspected and a normal appendix is found, it is essential to examine the distal ileum for Meckel's diverticulum.

Trauma—Any discussion of acute abdominal emergencies in children must include acute trauma. The large number of automobile accidents as well as the common accidents in the playground and the home subject many children to abdominal trauma. Crushing injuries may cause rupture of a hollow viscus. Intra-abdominal hemorrhage can result from lacerations of the liver, spleen or mesentery. Penetrating abdominal wounds always necessitate surgical exploration.

Diagnosis of acute intra-abdominal injury is based on a history of trauma, abdominal rigidity, tachycardia, shock, shoulder pain, and roentgenologic evidence of free air in the abdominal cavity. When intra-abdominal bleeding is suspected, peritoneal tap should be done. Whenever one suspects intra-abdominal injury, immediate laparotomy is indicated.

Physical Examination of the Heart

A CONVENIENT, HIGHLY INFORMATIVE AND OFTEN NEGLECTED MEANS OF CARDIAC DIAGNOSIS

PARK W. WILLIS, III, MARY E. CLIFFORD AND FRANKLIN D. JOHNSTON*

University of Michigan Medical School, Ann Arbor

There are no clinically applicable graphic methods which will conveniently substitute for careful physical examination of the heart. This examination includes pertinent portions of the general physical examination, inspection of the precordium, palpation of the anterior and lateral surfaces of the chest wall, percussion of the heart border, and auscultation over the heart and great vessels and elsewhere when indicated. Physicians who are aware of the important observations which have resulted from laboratory study of heart sounds and murmurs and precordial movements associated with the heart beat are well equipped to gain skill in the useful technics of physical examination of the heart. The major pitfalls are inexact methods of observation and prematurity of conclusion.

PARK W. WILLIS, III

THE trouble with doctors is not that they don't know enough, but that they don't see enough." We would modify this 100 year old statement of Sir Dominic J. Corrigan to read: "The trouble with doctors is not that they don't know enough, but that they don't see, feel or hear enough."

The physical examination of the heart as it is usually performed rarely discloses all the information that is available to the physician at the bedside. Fortunately we are now experiencing what might be termed the renaissance of the physical examination of the cardiovascular system. This has been brought about largely by studies correlating physical findings, particularly heart sounds and murmurs and low-frequency vibrations, with the hemodynamic and electric events in the cardiac cycle. Physicians interested in cardiac diagnosis are becoming aware that they have at their command three precision instruments of great versatility and of enormous value. These tools, of course, are the eyes, hands and ears.

In many of the common types of congenital

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MARY E. CLIFFORD

FRANKLIN D. JOHNSTON

heart disease, especially in adults, and in valvular disease of rheumatic origin, an accurate diagnosis often is established by the physical examination and subsequently supported or confirmed by other methods of cardiac evaluation. A large group of patients, however, have lesions of such mild degree that the diagnosis can be suspected or established *only* from the physical examination; by all other methods of evaluation the heart may appear normal. In addition, certain information about the pathologic anatomy of the diseased heart, especially that pertaining to the physical characteristics of the valve leaflets, can be obtained *only* by the physical examination.

There is a tendency among physicians, including many cardiologists, to ignore or minimize the information available from the physical examination in deference to that obtained by more exotic methods because of a feeling that the physical examination, although adequate from a qualitative point of view in most cases, is not sufficiently quantitative. There is certainly little question that if one wishes to make "exact" calculations of flows, resistances and volumes, data are necessary which are obtainable only by cardiac and arterial catheterization. However, from the clinical point of view of caring for an individual patient there is considerable question in our minds whether the physical examination, carefully performed and coupled with an adequate history obtained from a reliable patient, may not be as satisfactory and often as quantitative as the more highly refined studies. In another large group of patients the history will give the main evidence of heart disease by revealing symptoms of cardiac pain or of heart-failure, and abnormal physical findings may be absent or limited to cardiac enlargement and signs of congestive heart-failure. In these instances more exact evaluation may be possible by other studies, principally the simple ones, the electrocardiogram and the x-ray examination of the heart.

It is our purpose here to emphasize those areas in which the physical examination is apt to provide definite information as to the nature of the heart disease, possibly allowing the patient to avoid the expense of time and money and the physical discomfort and inconvenience of cardiac catheterization, angiocardiography or other special studies. It must be emphasized, however, that much of the information which is available today confirming the value of the physical examination has been obtained through the use of these highly specialized technics.

Most students, and many physicians, tend to think of the physical examination of the heart only in terms of the location of the apex beat and the left border of cardiac dullness, and, more particularly, in terms of the auscultatory findings. However, a complete examination of the heart includes pertinent portions of the general physical examination, inspection of the precordium, palpation of the anterior and lateral chest wall, percussion of the heart border, and auscultation over the heart and great vessels and elsewhere when indicated.

Pertinent Aspects of the General Physical Examination

The general physical examination should include observation of the patient for extracardiac congenital abnormalities and for evidence of underdevelopment, either of which may be associated with congenital cardiac defects. It should also include inspection of the skin for lesions associated with heart disease, such as those due to hypercholesteremia, myxedema and subacute bacterial endocarditis; inspection of the hands for clubbing of the fingers, and of the mucous membranes and nail beds for evidence of cyanosis; visualization of the vessels of the ocular fundi; evaluation of the venous system, including the

venous pulsations of the neck, estimation of the gross venous pressure, and a search for the hepatojugular reflux; and palpation of the accessible arterial pulses.

Inspection of the Precordium

Inspection of the chest wall overlying the heart is an important preliminary to the rest of the cardiac examination. Congenital heart disease, when associated with right ventricular hypertrophy, may produce an outward bulge of the chest wall. A pectus excavatum deformity may displace the heart and great vessels to the left and thus be a cause of apparent cardiac enlargement both by physical examination and by x-ray, and may result in a systolic murmur which, if located in the pulmonic area, is commonly mistaken for one resulting from organic heart disease, especially atrial septal defect. A visible apex impulse on the right side of the chest would be a clear indication of dextrocardia. A visible and diffuse apex beat evident lateral to the usual position is indicative of dilatation of the left ventricle. Outward movement of the precordium may be evident in diastole in cases of restrictive endocardial, myocardial or pericardial disease, especially the latter, or in instances of extensive myocardial fibrosis. An outward movement in systole may be visible in some persons with ventricular aneurysm.

Palpation of the Chest Wall

Following inspection of the chest, the anterior and left lateral portions of the chest wall should be palpated thoroughly and at a leisurely pace with the hand lightly applied. This highly informative and almost universally neglected part of the cardiac examination allows analysis of the low-frequency movements of the chest wall. This is helpful in the determination of hypertrophy or dilatation of the cardiac chambers or dilatation of the great vessels, and careful palpation also may reveal loud sounds manifested as shocks and loud murmurs as thrills. Information secured by inspection and palpation, especially pertaining to ventricular hypertrophy, may be unobtainable by other means and of critical importance in diagnosis.

A knowledge of the normal movements of the chest wall is important here and can best be obtained by making this procedure an integral part of every physical examination. In youth, fairly prominent pulsations may be encountered normally over the right ventricle (parasternal area), the left ventricle (apex beat), and even over the pulmonary artery (second left intercostal space at the sternal border). These pulsations tend to decrease with age and to be obliterated by emphysema, severe spondylitis, or other situations which limit mobility of the chest cage. Shocks and thrills are the palpatory evidence of events which are easily audible and are therefore not as important as the impulses of very low frequency associated with left and right ventricular hypertrophy or dilatation, acute myocardial infarction or ventricular aneurysm, dilatation or aneurysm of the aorta or pulmonary artery, and presystolic and protodiastolic impulses which at times may be felt but not heard.

With the patient in the supine position, the hand is first placed on the chest wall in the low parasternal area to determine whether or not there is an abnormal precordial lift over the right ventricle. This is more prominent when produced by conditions resulting in dilatation as well as hypertrophy of the right ventricle, especially in situations such as atrial septal defect where there is a high volume of blood flow through the right ventricle. When there is hypertrophy without much chamber dilatation the precordial lift may seem quite normal, particularly in some instances of isolated congenital pulmonic stenosis.

The examiner should next determine the location of the apex impulse with the patient supine and in the left lateral position. This is best accomplished by letting the fingers of the right hand lie in the rib interspaces over the apex impulse. When it has been located, palpation with one or two fingers can be carried out to study its characteristics. The normal left ventricular apical impulse is small in area, about the size of a nickel or quarter, and tapping in character. When the apex beat is very forceful or unduly sustained, left ventricular hypertrophy or dilatation can properly be suspected, and the latter condition is likely to

be present if the point of maximal impulse is displaced to the left. Care must be taken not to confuse the impulse of a greatly dilated right ventricle with that due to left ventricular hypertrophy. A prominent apex beat is present in this situation, but careful examination will show that it is continuous with the parasternal lift and therefore related to right ventricular contraction. The implications of this error in patients with mitral valvular disease are serious, for if one suspected left ventricular hypertrophy in a patient with "pure" mitral stenosis, coexistent aortic valvular disease, mitral insufficiency or arterial hypertension would be postulated.

With right ventricular failure an early diastolic impulse often may be felt over the right ventricle. This must not be mistaken for the diastolic outthrust of constrictive pericarditis, and at times the differentiation is quite difficult. When the left ventricle is in failure or close to it for any reason, a presystolic impulse often can be palpated at the apex, presenting itself as the first portion of a double apex impulse.

Palpation in the two areas mentioned is of primary importance, but the tricuspid, aortic and pulmonic areas also should be examined for outthrusts, shocks or thrills. In the second interspace at the left sternal edge, pulsations from the pulmonary artery may be appreciated, and pulsations from a dilated aorta may be evident in the second or first intercostal space on the right or over the right sternoclavicular junction.

Percussion

This method of cardiac examination is so generally employed that it needs little comment. The method is an accurate one to determine heart size in all except very obese persons and those with a marked increase in the anteroposterior diameter of the chest, often associated with pulmonary emphysema. The direct method of percussion, where the tips of the middle and ring fingers of the right hand strike the precordium with quick but gentle blows, is of particular value in estimating heart size, but the conventional bimanual technic usually should be used also.

Auscultation of the Heart

Although competence and self-confidence in auscultation are developed only with considerable effort and after much experience, there are a number of fairly simple things any physician can do to make the job easier and more productive. It is wise to be sure the patient is comfortable, that he is not cold, and that he is not unnecessarily exposed to the view of others. When examining patients with orthopnea it is important to raise the head of the bed. Similarly when the patient is in the left lateral position a pillow for back support is usually appreciated. Most women prefer not to be exposed if exposure can be avoided, and for this reason a small hand towel placed over the chest is a useful accessory during auscultation. The patient's comfort is not the sole consideration, however, and the wise physician will also assure his own comfort insofar as possible.

The environment, by presenting distracting or masking noise, is another important variable regulating the success of cardiac auscultation. Before listening to the heart of any patient one should be sure all extraneous noises are minimized. It may be easier to move the patient to a quiet room than to obtain silence in the immediate environment.

Certain comments should be made concerning the stethoscope itself. Experience has shown that with an instrument that fits comfortably and is equipped with a bell as well as a diaphragm the physician will, with practice, be able to hear almost everything of importance. Ideally the bell should be fairly shallow and not too large in diameter, and the interior diameter of the stethoscope tubing and binaural branches should not be large. Low-pitched sounds and murmurs are best heard with the bell applied lightly to the skin and may, in fact, be obliterated if the bell is placed firmly to the skin, in effect creating a diaphragm. By the latter maneuver, however, many high-pitched murmurs, even when quite faint, may be heard as well with the bell as with the diaphragm. The vast majority of heart sounds and murmurs can be heard if one uses the stethoscope with only the bell

endpiece, and we do not hesitate to urge its almost exclusive use in listening to the heart. Except for physicians with defective hearing there seems to be little advantage in the use of any of the several types of electronic amplifying stethoscopes currently available.

For completeness in listening to the heart the examiner must be systematic in his approach. This applies to the analysis of what is heard in each area of the precordium, to the areas of the precordium that are examined, and to the different positions in which the patient is placed during the examination. The patient should be examined not only in the supine position but also in the left lateral and sitting positions, often leaning forward with the breath held in expiration. In each of these positions, but especially when the patient is supine, the examiner must again be systematic by following a routine plan for listening to the heart. Usually emphasized are the locations in which the sounds and murmurs from a particular valve are apt to be heard best. Thus, auscultation usually is carried out at the aortic, pulmonic, tricuspid and mitral valvular areas, but if examination is limited to these specific points some phenomena will be missed completely and others heard at reduced intensity. Accordingly, for completeness it usually is necessary to listen at a number of intermediate points. In general, in the past, too little attention has been paid to the area of the tricuspid valve.

The human ear has a marvelous power of discrimination, and this quality should be used fully during auscultation. When the examiner is listening for the heart sounds, he must ignore any extra sounds or murmurs that may be present. As Dr. Samuel A. Levine has emphasized so well, the key to successful auscultation of the heart lies in listening for (and hearing) only one thing at a time.

The rate and rhythm of the heart should be studied first. This is important because careful auscultation, sometimes noting the effects of exercise, stimulation of the carotid sinus, or other procedures, usually will allow the examiner to make a clinical diagnosis of any arrhythmia present. Occasionally a burst of tachycardia or other arrhythmia may occur while the heart is being examined and provide a valuable clue to previously unexplained symptoms such as palpitation, nonanginal chest discomfort, angina pectoris, syncope, weakness or dyspnea, any of which in certain circumstances may result from a paroxysmal arrhythmia.

The examiner should next observe the intensity, pitch and splitting of the first and second heart sounds. Heart sounds should be recorded as normal, decreased or increased in intensity, and sharp or dull in quality, and comment should be made regarding splitting and its relationship to the respiratory cycle. These observations give information relative to the physical characteristics of the valve leaflets, the pulmonary arterial pressure and to a lesser extent the systemic arterial pressure, and, occasionally, the presence or absence of intraventricular conduction defects.

Next the observer should listen carefully for extra sounds in systole and in diastole. With very rapid rates the correct timing of extra sounds often is more accurately carried out by identification of a characteristic cadence or triple rhythm than by exact analysis of the sound itself. In addition to determining the position in the heart cycle, variation in intensity of these sounds during the respiratory cycle should be noted.

Next, attention should be directed to systolic and diastolic murmurs. In recording the findings pertaining to heart murmurs, loudness may be less important than duration, variation in intensity from instant to instant, relation to the first and second heart sounds, quality and certain other characteristics.

If such a system for the detailed analysis of the auscultatory events of the heart cycle is used regularly, one will soon find that he is able to recognize certain characteristic combinations of murmurs and sounds as representative of certain pathologic conditions. This is done in much the same fashion as an experienced reader learns to recognize complete phrases or even sentences at a glance rather than by reading each individual letter. Listening by phrase, so to speak, is a convenient and easy method once one has had the necessary background and experience.

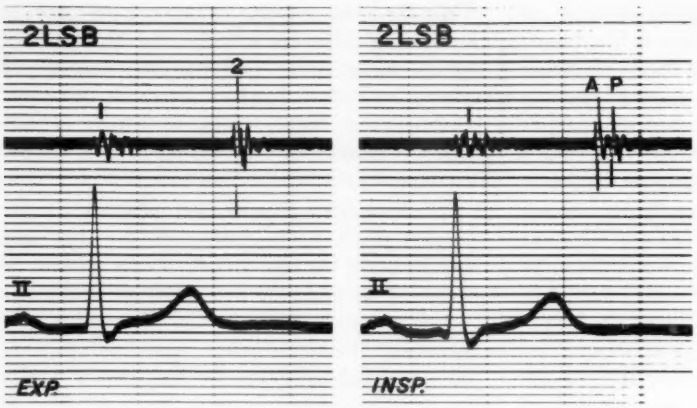

FIGURE 1. Physiologic splitting of the second heart sound (pulmonic area). The aortic (A) and pulmonic (P) components of the second sound (2) can be heard separately as a split sound with normal delay of pulmonic valvular closure during inspiration.

Certain auscultatory features of the normal heart deserve emphasis. The first heart sound has two major components representing closure of the mitral and tricuspid valves. Splitting of the first heart sound is common, does not exceed 0.03 second, and usually is best heard in the tricuspid area. At the apex of the heart the first sound usually is louder but lower pitched than the second sound. At the base of the heart the second sound, produced by closure of the pulmonic and aortic valves, is louder than the first sound and splits during inspiration (figure 1). This splitting is due to delayed closure of the pulmonic valve, probably related to increased filling of the right ventricle during inspiration, and is heard best at or close to the pulmonic area. This same mechanism accounts for the commonly observed increase in intensity or pitch of sounds and murmurs arising from the right side of the heart during inspiration. In youth the second sound is louder in the pulmonic area than in the aortic area, but this relationship often is reversed in early adult life. In most normal young persons a sound in early diastole, the physiologic third heart sound, can be heard at the apex (figure 2). This sound, very low in pitch, is best described as a dull thud and probably arises in the ventricular wall as blood enters from the atrium early in diastole.

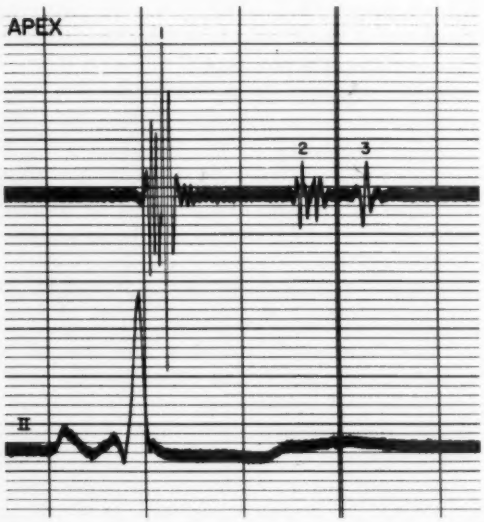

FIGURE 2. Physiologic third heart sound (apex). This sound, a "dull thud" (3), occurs in early diastole during rapid ventricular filling. It can be heard in most normal young persons, especially after exercise and immediately after assuming the recumbent position.

In the presence of heart disease the character of the first heart sound may change. With hypertensive, aortic valvular or degenerative heart disease the first sound frequently becomes quite faint and may be preceded by an atrial or a presystolic extra sound. Conversely, in the presence of mitral stenosis the first heart sound often becomes sharp and snapping, when minimal fibrotic thickening of the valve leaflets occurs without extensive scarring or calcification. This first sound in combination with the presystolic murmur of mitral stenosis presents a characteristic sound complex (fig-

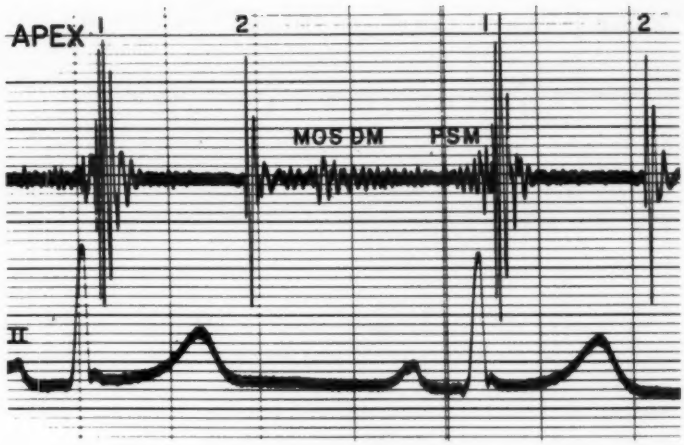

FIGURE 3. Mitral stenosis with normal sinus rhythm (apex). The mitral opening snap (MOS) is followed by a long diastolic murmur with characteristic early (DM) and late or presystolic (PSM) accentuation, the latter terminating in a loud, snapping first heart sound (1).

ure 3). A loud, snapping first heart sound at the apex, particularly if heard in a patient with atrial fibrillation, pulmonary hypertension or unexplained heart-failure, should lead one to search carefully for other evidence of mitral stenosis. Fever, tachycardia and thyrotoxicosis also increase the intensity of the first sound by increasing the rate or force of valvular closure or the excursion of the valve leaflets. A decrease in the loudness of the first sound may occur with first-degree atrioventricular (A-V) heart block, extensive degenerative heart disease or mitral insufficiency with marked valvular deformity and leaflet immobility. In the absence of the latter two conditions this finding is a fairly reliable sign of first-degree A-V heart block if the first sound is constant in intensity, and of complete heart block if the rate is slow and the first sound varies in intensity. A loud, often snapping first heart sound can be heard in the tricuspid area in patients with pulmonic stenosis, atrial septal defect, or other causes of marked right ventricular hypertension.

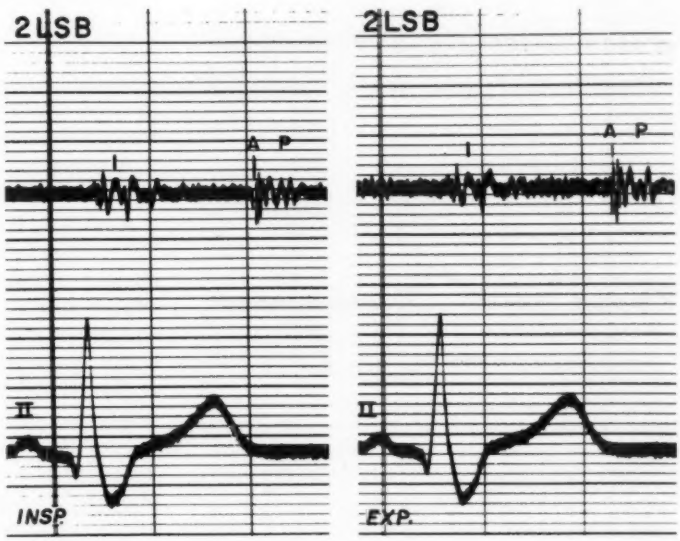

FIGURE 4. Complete right bundle-branch block (pulmonic area). Wide, fixed splitting of the second sound occurs since the prolonged activation of the right ventricle delays closure of the pulmonic valve (P). In some patients the splitting is more prominent during inspiration.

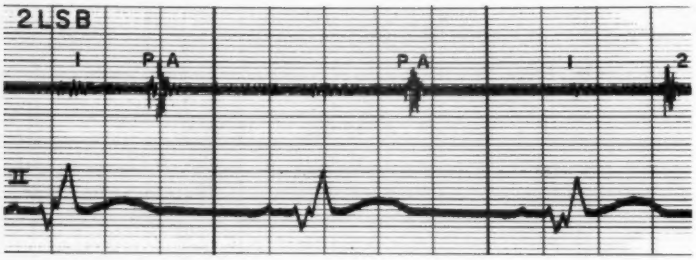

FIGURE 5. Complete left bundle-branch block (pulmonic area). Paradoxical splitting of the second sound, splitting during expiration (at left), occurs, since closure of the aortic valve (A) is delayed at all times by the prolonged activation of the left ventricle while closure of the pulmonic valve (P) varies normally with respiration and occurs later during inspiration (at right).

Splitting of the second heart sound is of interest to the clinician, since it may lead one to suspect the presence of an intraventricular conduction defect. Complete right bundle-branch block, by delaying the completion of right ventricular systole, causes the splitting of the second sound in the pulmonic area to persist during expiration, although further widening may still be noted during inspiration (figure 4). The presence of left bundle-branch block may be suspected clinically when "paradoxical" splitting, splitting only during expiration, occurs (figure 5). Paradoxical splitting has also been described in congenital or acquired defects which prolong left ventricular ejection time (patent ductus arteriosus and aortic stenosis). Other factors which lead to an increased degree of splitting are those which delay the pulmonic valve closure or allow early closure of the aortic valve. Some of the most impressive examples of delay in closure of the pulmonic valve are found in patients with pulmonic stenosis (figure 6). Here the pulmonic component of the second sound may be very late but often is quite soft and not readily discernible by auscultation. Atrial septal defect or anomalous pulmonary venous return, with a left-to-right shunt, characteristically leads to wide splitting of the second sound (figure 7) that is "fixed" throughout both phases of respiration. This splitting may be well heard at the apex, where the pulmonic component usually is not audible. Mitral insufficiency and interventricular septal defect (figure 8) also may lead to wide splitting because of shortened left ventricular ejection time and the earlier closure of the aortic valve.

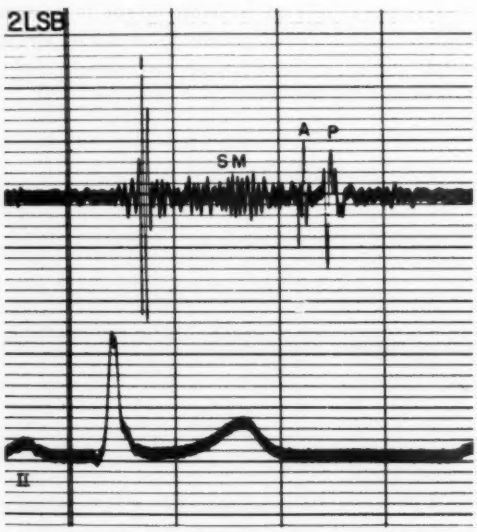

FIGURE 6. Mild pulmonic stenosis (pulmonic area). A systolic ejection murmur (SM) is present and there is wide splitting of the second sound (A, P) as a result of prolonged ventricular systole. The pulmonic component (P) is quite loud here as the stenosis is mild. In severe stenosis, with a low pulmonary arterial pressure, the pulmonic component often is inaudible.

A gallop rhythm is said to be present when there are three heart sounds and the heart rate is over 100. It is important to go beyond the mere recognition of this rhythm and to attempt to determine the exact location of the extra sound in the cardiac cycle. Both systolic and diastolic extra sounds may produce a gallop or triple rhythm. Use of the carotid pulse or the second heart sound for timing is often helpful.

Diastolic triple rhythms are produced by the addition of an early (protodiastolic) sound or of a late (presystolic) sound to the first and second heart sounds. Both of these dia-

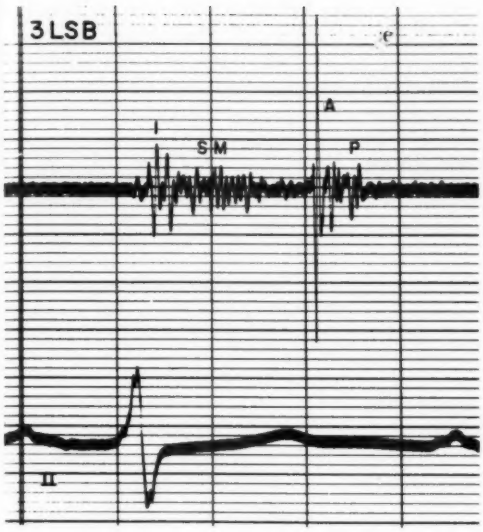

FIGURE 7. Atrial septal defect with left-to-right shunt (third interspace, left sternal border). A systolic ejection murmur (SM) is noted with fixed splitting (A, P) of the second sound. The murmur usually is superficial and scratchy in quality and shorter than that of pulmonic stenosis. The splitting may disappear if severe pulmonary hypertension develops.

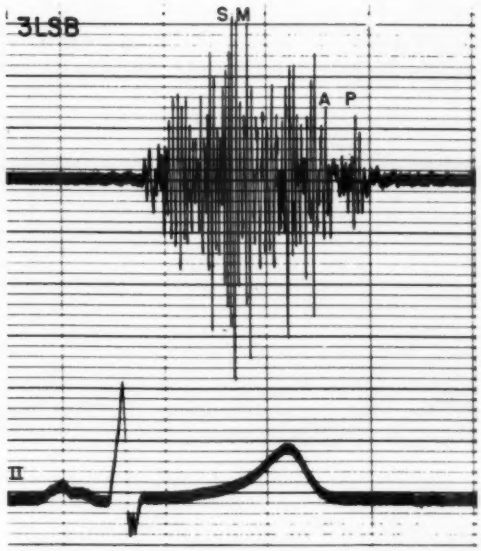

FIGURE 8. Ventricular septal defect with left-to-right shunt (third interspace, left sternal border). This harsh pansystolic murmur (SM) is quite loud in adults and often is associated with a thrill. The presence of severe pulmonary hypertension may alter the timing and quality of the murmur.

stolic extra sounds are typically low-pitched, low in intensity and "thudding" in quality. The protodiastolic extra sound, sometimes called a ventricular filling sound, occurs immediately after the opening of the mitral and tricuspid valves and is heard most commonly over the right ventricle in situations which produce an elevated systemic venous pressure or increased flow through this chamber. A left ventricular protodiastolic extra sound is a characteristic finding in mitral insufficiency (figure 9). A protodiastolic extra sound is often associated with early heart-failure. A very loud sound of this type which may be quite sharp and high-pitched is found in chronic restrictive pericardial disease and occurs at the time of the characteristic sudden termination of the early diastolic phase of ventricular filling.

Presystolic or fourth heart sounds are present commonly in situations where there is increased resistance to ventricular ejection, as in systemic or pulmonary arterial hypertension and aortic or pulmonic valvular stenosis. They

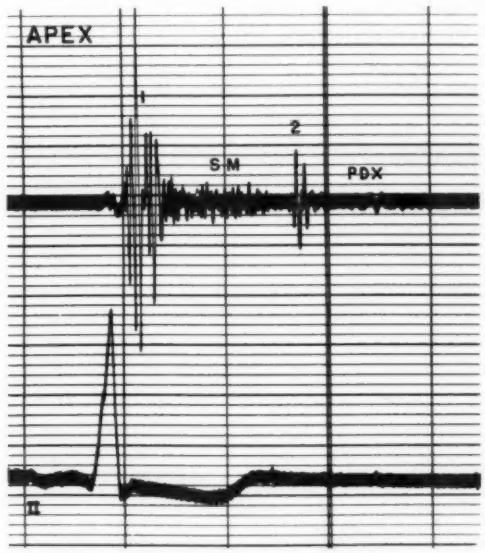

FIGURE 9. Mitral insufficiency of minor degree with a protodiastolic extra sound (apex). When the valvular lesion is severe this low-pitched sound (PDX) usually is found in association with a diminished first sound and a loud pansystolic murmur.

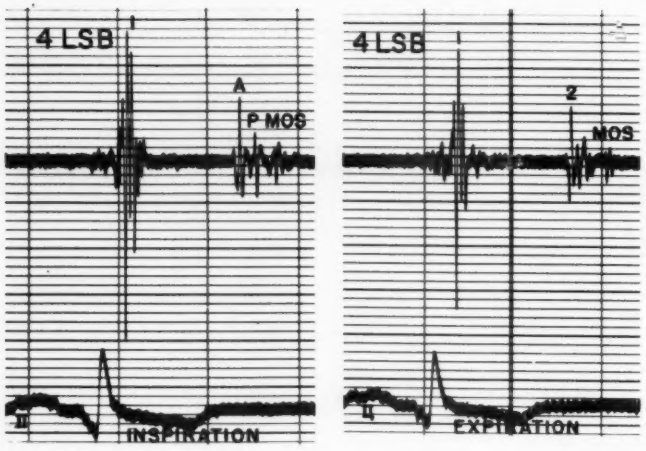

FIGURE 10. Mitral opening snap (fourth interspace, left sternal border). Detection of this sound (MOS) should prompt a thorough search for the murmur of mitral stenosis. The opening snap is heard most distinctly during expiration when there is no marked splitting of the second sound (2).

also may be heard fairly frequently following myocardial infarction or in the presence of first-degree A-V block. These diastolic extra sounds usually are of very low frequency and often can be appreciated better by palpation than by auscultation. In general they have no great prognostic significance.

The mitral opening snap is of considerable importance in the prediction of successful mitral valvular surgery. Its production depends on the presence of relatively pliant, mobile valve leaflets. When this sound is heard in a patient who is thought to have "pure" mitral stenosis, one can be fairly certain the surgeon will not encounter extensive scarring and calcification of the valve. In addition if a successful commissurotomy can be performed it would be expected that the closest approximation to normal valve leaflet function would be obtained in such patients.

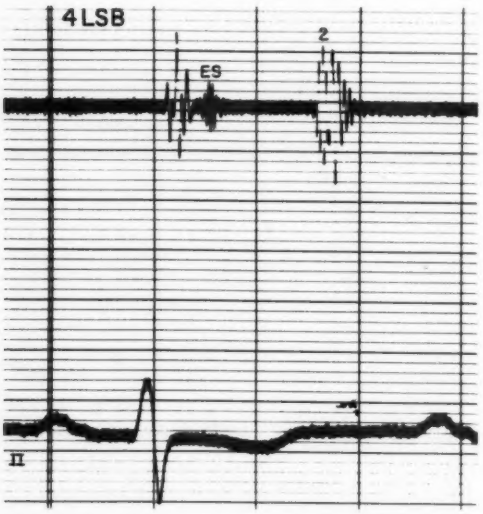

FIGURE 11. Systolic ejection sound (fourth interspace, left sternal border). Although similar to an insignificant systolic click, this sound (ES) was recorded from a patient with severe pulmonary hypertension and probably had its origin in the wall of the pulmonary artery.

The mitral opening snap is heard best medial to the apex and along the left sternal border and typically is very high-pitched. It may be well transmitted to the base of the heart and at times must be distinguished from a split second sound or a protodiastolic extra sound. The mitral opening snap has a fixed position in relation to the second heart sound or, if variation occurs, appears to be more widely separated from the second sound during expiration (figure 10).

Extra sounds in early systole are particularly interesting. While many of them seem to be of extracardiac and extravascular origin and have absolutely no relation to heart disease, some may represent an accentuated "vascular component" of the first heart sound. In this case they may have their origin in the aorta or pulmonary artery and are heard best at the base of the heart over these vessels, although aortic "ejection sounds" often are transmitted well to the apex. These sharp clicking sounds

frequently are mistaken for loud first heart sounds, particularly in the presence of mild valvular stenosis when they occur very early in systole. In the latter situation a sound of this type may be an "opening snap" of a mildly stenotic aortic or pulmonic valve, whereas in the presence of a dilated aorta or pulmonary artery the sound probably is produced in the wall of the great vessel itself as it reaches its limit of distensibility early in systole (figure 11). Some of the more common lesions with which these sounds are heard are aortic insufficiency, mitral stenosis with pulmonary hypertension, systemic arterial hypertension with dilatation of the aorta, aneurysm of the aorta, mild pulmonary or aortic stenosis, atrial septal defect, and tetralogy of Fallot.

Extra sounds which occur most frequently in mid or late systole (figure 12) and which have a somewhat superficial quality as if "close to the ear" are not of clinical significance and probably are all of extracardiac origin. They may be related to pleuropericardial adhesions, and sometimes are associated with very late loud systolic murmurs of unusual quality. It is extremely important to recognize these "clicks" as insignificant in order to avoid the production of iatrogenic heart disease. Late systolic clicks have been noted following operations involving opening the pericardium.

Correct interpretation of a heart murmur depends on analysis of its quality and timing. Since quality includes such factors as frequency, intensity and musicality, it is poorly represented in phonocardiographic tracings. It is by its quality that the clinician recognizes a murmur, in much the same fashion that he identifies a voice or a bird's song. Bourne has captured the quality of the murmur of aortic stenosis in the following statement: "The sound here suggests the deliberate forceful and short blasts of steam given off by the Scottish express starting from rest at King's Cross." The term "whistling" often is applied to the murmur of mitral insufficiency, and "rumbling" to that of mitral stenosis.

In regard to timing, the classification suggested by Leatham is useful. Systolic murmurs may be divided into ejection and regurgitant

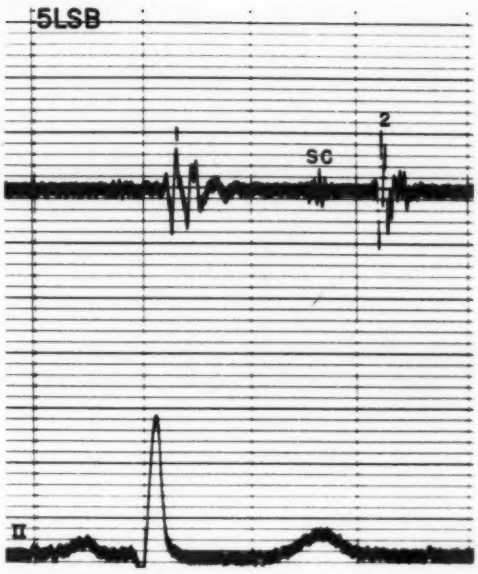

FIGURE 12. Systolic click (SC) (fifth interspace, left sternal border). This finding, of extracardiac origin, is of no clinical significance but is commonly misinterpreted as a pathologic sound, especially when the heart rate is rapid so that a gallop rhythm is produced.

murmurs. Regurgitant murmurs are produced by blood flow from a high-pressure chamber to a low-pressure chamber, as from ventricle to atrium or from left ventricle to right ventricle. Because of the pressure relationships such a murmur extends throughout systole, running into and sometimes obscuring both the first and second heart sounds. Mitral and tricuspid insufficiency and interventricular septal defect, as long as the major shunt is from left to right, produce this type of murmur. The ejection type of murmur, on the other hand, is produced at the aortic or pulmonic valve and is midsystolic in timing. Because of the period of isometric systole, the onset of the murmur is delayed until slightly after the first heart sound. After the period of rapid systolic ejection, forward flow through the valve declines quickly and the murmur invariably ends before the component of the second heart sound originating from the affected valve (figure 13). Ejection murmurs at the pulmonic and aortic valves can be attributed to several different factors which are

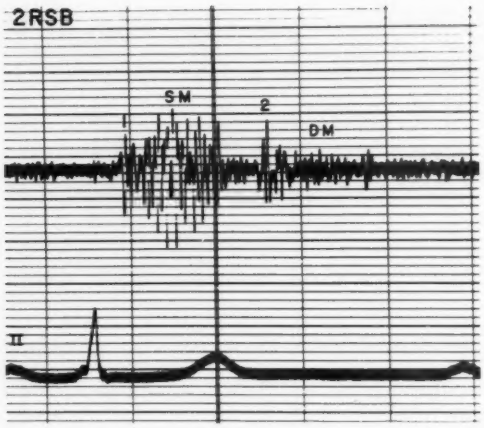

FIGURE 13. Aortic stenosis and insufficiency (aortic area). The diamond-shaped ejection murmur of aortic stenosis (SM) is here recorded with the high-pitched decrescendo murmur of aortic insufficiency (DM). This combination of two murmurs of different quality resembles the sound of "sawing wood" and must be distinguished from the single continuous murmur of patent ductus arteriosus, which starts after the first sound, builds up before and extends through the second sound into or through diastole.

common to the production of all murmurs: increased blood flow through a normal orifice, dilatation of the vessel beyond the valve, actual narrowing or stenosis of the valve, and valvular deformity without significant stenosis. A midsystolic murmur of uncertain cause may be heard normally over the pulmonary artery in young persons and over the aorta in the elderly. Atrial septal defects produce loud, superficial or scratchy ejection murmurs in the pulmonic area by increasing flow through the pulmonary artery. Valvular stenosis causes a somewhat longer and coarser murmur which often is associated with a thrill. In the presence of stenosis there is delayed closure of the involved valve, and the murmur may extend through the closure sound of the uninvolved valve. If the stenosis is mild, careful auscultation may allow one to hear the delayed soft component of the second sound originating in the involved valve.

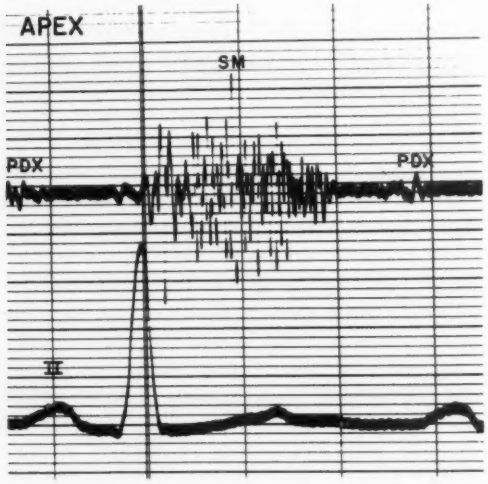

FIGURE 14. Mitral insufficiency (apex). The pansystolic regurgitant murmur (SM) extends from the first to the second heart sound, obscuring both to some degree, and is followed by a loud protodiastolic extra sound (PDX).

The murmur of aortic stenosis often is heard well at the apex of the heart, and the murmur of mitral insufficiency may be confused with it if, as frequently occurs, the second sound is inaudible at the apex and the loud protodiastolic extra sound usually present is mistaken for the second heart sound (figure 14).

A method which has been suggested to differentiate the murmur of aortic stenosis and that of mitral insufficiency is the inhalation of amyl nitrite. With this maneuver the murmur of mitral insufficiency becomes less loud while that of aortic stenosis increases in intensity, presumably because of decreased peripheral vascular resistance with an increased forward flow through the aortic valve.

Occasionally the murmur of an atrial septal defect is quite intense and associated with a thrill. This leads to confusion with an interventricular septal defect. In this situation the timing of the murmur as already described will be particularly helpful.

Diastolic murmurs also have been divided into two general types, the arterial diastolic murmurs of aortic and pulmonic insufficiency and the atrioventricular murmurs of mitral and tricuspid stenosis. The arterial diastolic murmurs begin with the second sound, and, as graphically described by Bourne, have a "high pitched rushing and persistent quality of water escaping under pressure from a hose, over a weir, or from a leaky lock gate." These

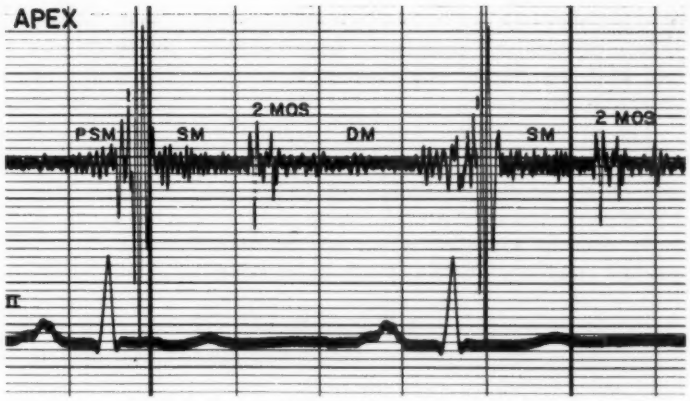

FIGURE 15. Mitral stenosis and insufficiency (apex). The presence of the loud, snapping first sound (1), the mitral opening snap (MOS), and the murmur throughout diastole (DM, PSM) indicates that mitral stenosis is the important lesion. The opening snap follows the second heart sound (2) by a short interval, suggesting that left atrial pressure is quite high so that the mitral valve opens before right ventricular pressure reaches its minimum. In mild mitral stenosis (figure 3) the opening snap follows the second sound by a longer interval.

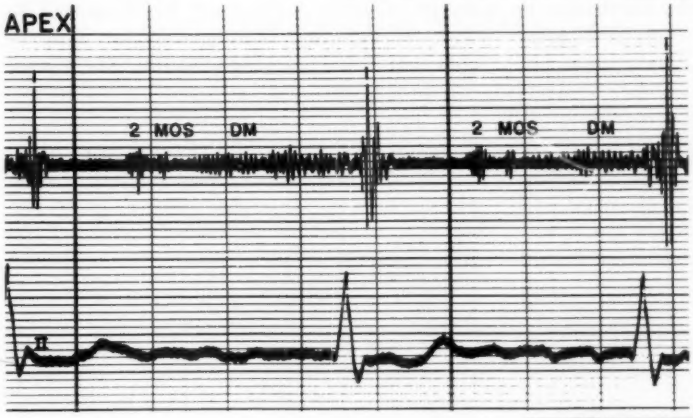

FIGURE 16. Mitral stenosis with atrial fibrillation (apex). The diastolic murmur (DM) extends throughout diastole but presystolic accentuation, dependent on normal atrial contraction, is not present.

murmurs, apt to be overlooked in a noisy room, are heard best with the patient sitting and leaning forward or in the left lateral decubitus position with the breath held in expiration. When heard to the right of the sternum the murmur probably arises at the aortic valve. Aortic diastolic murmurs also are well transmitted to the apex, where they can be distinguished from the diastolic murmur of mitral stenosis by timing and quality. Both the murmur of pulmonic insufficiency and that of aortic insufficiency usually are heard best along the left sternal border. To distinguish one from the other, one often must depend on the peripheral signs of aortic insufficiency or on findings suggesting pulmonary hypertension. Not uncommonly it is impossible to determine the exact source of a murmur of this type. This differential diagnostic problem

FIGURE 17. Functional systolic murmur (fifth interspace, left sternal border). This murmur (SM), vibratory in quality, is present only early in systole. When loud, a murmur of this type may be mistaken for that of ventricular septal defect. A physiologic third heart sound (3) also is present.

is especially common in patients with severe mitral stenosis and pulmonary hypertension, and in many clinical situations it is of considerable importance.

The presystolic murmur in tricuspid or mitral stenosis is produced by atrial systole and builds up in a crescendo fashion to the accentuated first heart sound (figure 15). The early diastolic murmur, which has the "low pitched rumbling quality of a wooden wheel barrow, trundled over cobblestones" (Bourne) starts after a short pause following the second sound and occurs during the period of rapid ventricular filling in early diastole. This is the only murmur heard if atrial fibrillation is present, since the presystolic murmur depends on effective atrial systole for its production. In the presence of marked valvular stenosis the early diastolic murmur will extend throughout the entire diastolic period (figure 16). A short murmur of this type may also be heard in patent ductus arteriosus and in atrial and ventricular septal defects, probably due to torrential flow across the tricuspid and mitral valves. This finding can lead to a mistaken diagnosis of rheumatic heart disease. The mitral diastolic murmur often can be heard only with the bell of the stethoscope and may be localized to a very small area at the apex of the heart. If the clinician suspects mitral stenosis he should examine the patient in the left lateral position after exercise. This maneuver may make the murmur audible when it cannot be heard otherwise. Tricuspid murmurs, both systolic and diastolic, characteristically become louder during inspiration, while mitral valve murmurs tend to become louder during expiration.

Functional systolic murmurs present extremely important and often difficult problems. When heard at the base of the heart they are of the ejection type, usually are not loud, and characteristically will almost completely disappear in the sitting position or with deep inspiration. A peculiar type of functional murmur heard along the left sternal border is early systolic in time and has a vibratory or grumbling or sometimes a musical quality (figure 17). Occasionally it is confused with the murmur of interventricular septal defect. The functional apical systolic murmur may be either early or late systolic in timing and does not have the characteristics of the murmur of mitral insufficiency already described. These functional apical systolic murmurs sometimes are associated with systolic clicks and usually are highly variable from one examination to the next.

Comment

The medical scientist engaged in any investigative effort is acutely aware of a basic principle which has been skillfully expressed by Sir Thomas Lewis: ". . . clinical pathology, by which I mean the study of disease in the living man, suffers both from *inexact observation* and from *hasty conclusion*. Many methods of clinical observation, being subjective, lack accuracy. Some subjective methods are commonly believed to be effective only in the hands of a chosen few; such methods, while always open to skepticism, never can be productive. Creditable methods of research are those capable of such description or demonstration that the intelligent and diligent may employ them to the end results which their originators claim for them. It is by this test primarily that methods are weighed in science; it is by this test also that clinical methods will be judged eventually."

Because of the remarkable versatility of the human senses, no clinically applicable graphic methods have been developed which will conveniently substitute for the careful physical examination of the heart. Therefore, the information which may be gleaned from practicing the art and the science of inspection, palpation, percussion and auscultation depends for the most part on an intelligent, interested and accurate examiner. Laboratory study of heart sounds and murmurs and of the precordial movements associated with the heart beat has resulted in a number of important observations regarding changes which occur in certain cardiac abnormalities. If the practitioner of medicine is aware of these observations he is well equipped to gain skill in these useful technics. The major pitfalls are *inexact methods of observation* and *prematurity of conclusion.*

What Radioisotopes Can Do for the Physician

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The 14 most common uses of radioisotopes in the Clinical Radioisotope Unit at University Hospital, Ann Arbor, Michigan, are outlined. The criterion for each is that the radioisotope can do a job that either cannot be done by existing methods or cannot be done as easily or as well. These uses of radioisotopes should be of aid to the physician in his everyday practice of medicine.

WILLIAM H. BEIERWALTES

WHEN a new diagnostic or therapeutic use of a radioisotope is proposed, it has been our policy to adopt it for routine use only if we believe it can do a job that cannot be done by existing methods, or at least not as easily or as well. The 14 most common uses of radioisotopes in the Clinical Radioisotope Unit at University Hospital are presented here with the hope that they may be of some aid to the practicing physician in diagnosis and treatment.

1. Diagnosis of Hypothyroidism While the Patient Is Taking Desiccated Thyroid

Administration of desiccated thyroid to a person with a normal thyroid gland alters all conventional diagnostic tests of thyroid function through the mechanism of depression of pituitary thyroid-stimulating hormone (TSH). Formerly it was necessary to stop the administration of desiccated thyroid for up to 16 weeks before conventional tests would accurately reflect the function of the thyroid gland. This delay is no longer necessary.

The patient is given 10 units of TSH on day 1, without stopping his thyroid medication. A tracer dose of radioiodine (I^{131}) is given on day 2. On day 3 a count is made over the thyroid gland and compared with the activity of the original tracer dose (figure 1). The patient with a normal thyroid gland temporarily depressed by administration of desiccated thyroid will concentrate I^{131} normally

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FIGURE 1. Instrumentation for radioiodine (I^{131}) tracer test of thyroid function.

a. Counting of tracer dose in plastic "neck."

b. Counting made over patient's neck to determine the percentage of the administered tracer dose accumulated in the thyroid gland.

after receiving TSH. A patient with true hypothyroidism concentrates I^{131} subnormally.

2. Diagnosis of Hyperthyroidism or Hypothyroidism Under Other Conditions Precluding Conventional Tests

If a patient has a disease that produces dyspnea, the basal metabolic rate may be elevated in the absence of thyroid abnormality. If a patient is undernourished, the serum cholesterol level may be lowered in the absence of hyperthyroidism. If a patient has received inorganic or organic iodides, the uptake of I^{131} by the thyroid gland may be lowered and the serum protein-bound iodine concentration may be elevated if there is no thyroid disease present.

The uptake of I^{131}-labeled triiodothyronine by the red blood cells (the I^{131}-T^3 uptake test) will accurately reflect thyroid function under all these circumstances. The rationale for this test is that in hyperthyroidism the serum proteins hold added I^{131}-T^3 less avidly than they

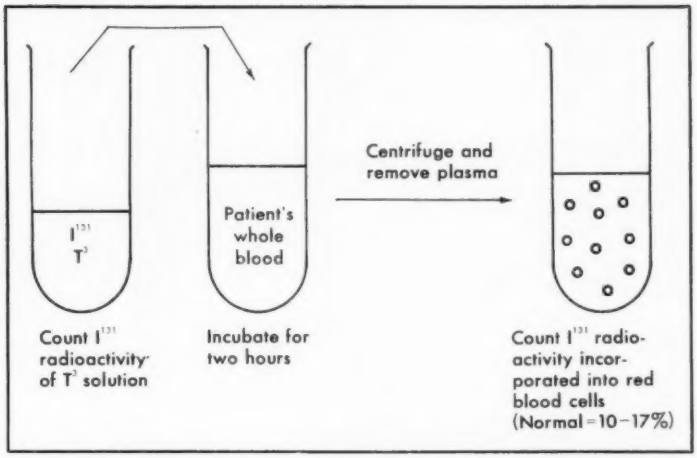

Centrifuge and remove plasma
I^{131} T^3
Patient's whole blood
Count I^{131} radioactivity of T^3 solution
Incubate for two hours
Count I^{131} radioactivity incorporated into red blood cells (Normal = 10–17%)

FIGURE 2. Diagrammatic representation of the technic of the I^{131}-T^3 red blood cell uptake test. Radioiodine-labeled triiodothyronine is added to the patient's whole blood in vitro. Hyperthyroid persons presumably concentrate more I^{131}-T^3 in the red blood cells because their plasma thyroxin-binding proteins have fewer available binding sites than do those of euthyroid persons.

From: Hamolsky, M. W. and associates. J. Clin. Endocrinol. 17:33, 1957.

do in euthyroidism. The reverse apparently is true in hypothyroidism. The radioiodine-labeled triiodothyronine is added to the patient's whole blood in vitro, as shown diagrammatically in figure 2, and the patient receives no irradiation.

3. *Detection of Functioning Thyroid Cancer*

The test to detect functioning thyroid cancer involves use of a machine called a scintiscanner (figure 3). Each recording gamma ray from a decaying atom of radioiodine is represented on a piece of paper as a dot. A concentration of dots is produced by a concentration of I^{131} in functioning thyroid tissue, benign or malignant. Figure 4 is a scintigram of a normal thyroid gland.

Figure 5 shows scintigrams in a case of adenocarcinoma of the thyroid. The record in figure 5a was made after a focus of thyroid carcinoma was removed by total right hemithyroidectomy and shows concentration of I^{131} only in the normal left lobe. The surgeon

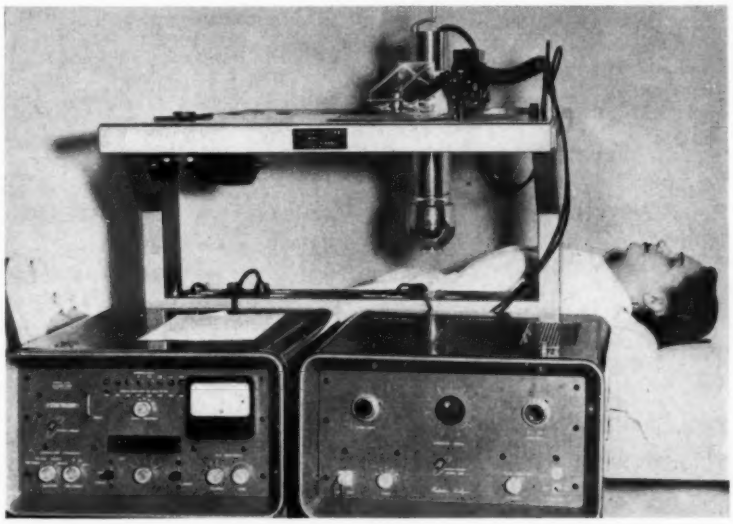


FIGURE 3. The scintiscanner. A scintillation detector tube hangs over the patient and is driven mechanically to produce a systematic "scan" of the relative concentration of I^{131} in the patient's body.

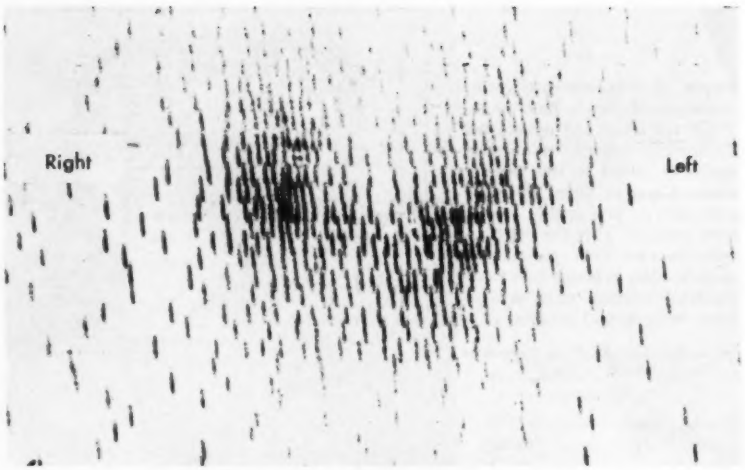


FIGURE 4. A scintigram drawn by the scintiscanner showing the concentration of I^{131} in a normal thyroid gland.

From: Clinical Use of Radioisotopes. Philadelphia, W. B. Saunders Company, 1957.

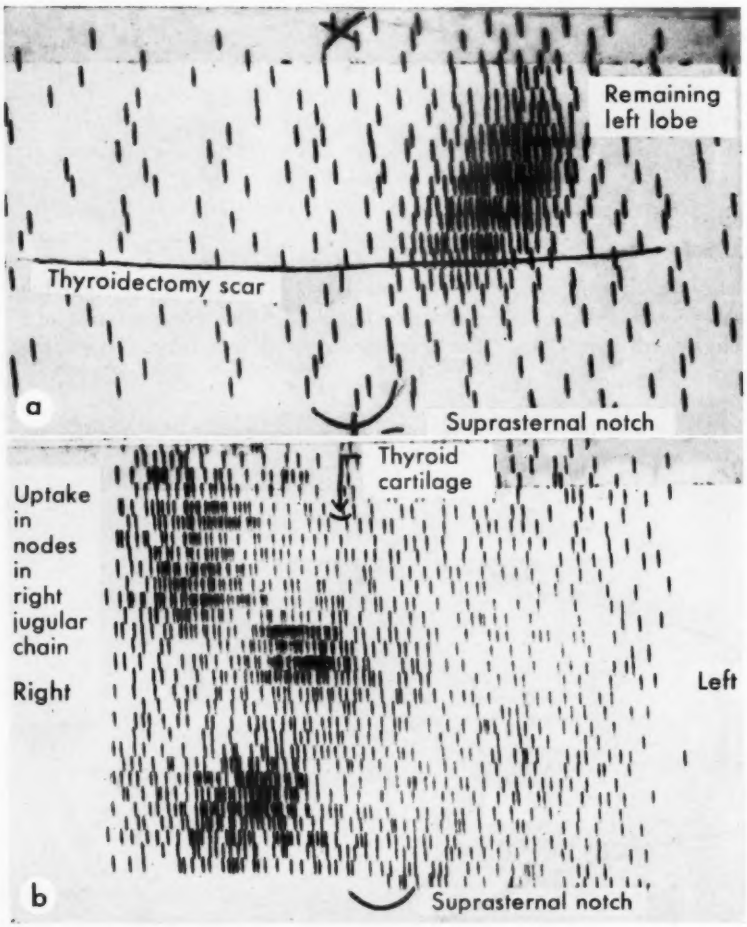
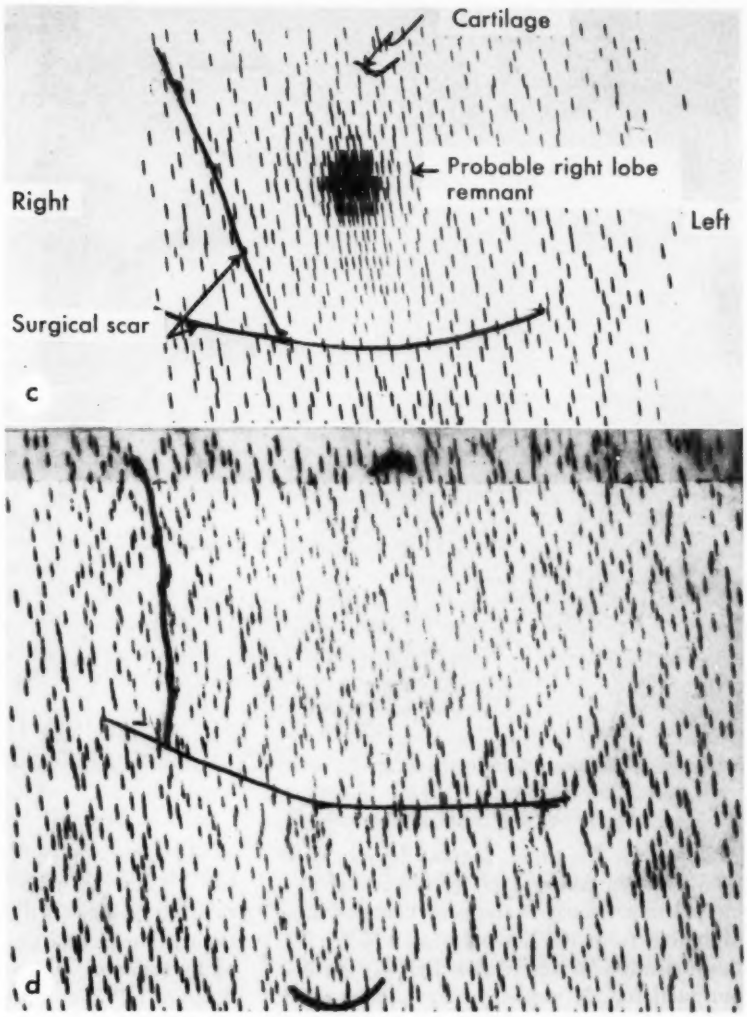


FIGURE 5. Scintigrams in a case of thyroid carcinoma. a. After total right hemithyroidectomy for nodular goiter. Pathologic report: papilliferous adenocarcinoma of the thyroid. Concentration of I^{131} in normal left lobe with no visible metastases in right jugular lymph node chain.

b. After total left hemithyroidectomy. Removal of left lobe permits demonstration of functioning thyroid cancer in right jugular lymph node metastases and in right lobe remnant.



c. After radical neck dissection on the right side, uptake in cervical node area is gone, confirming scintiscan impression. Residual uptake in remnant of "normal" right lobe. Surgeon was unable to find right lobe remnant.
d. Three months after treatment dose of I^{131} (100 millicuries). Total disappearance of functioning thyroid tissue.

From: Clinical Use of Radioisotopes. Philadelphia, W. B. Saunders Company, 1957.

looked for but was unable to find evidence of metastasis in the jugular lymph nodes in the right side of the neck. Total left hemithyroidectomy was performed subsequently, and figure 5b shows the scintigram obtained after the operation, with concentration of I^{131} in the upper and lower right jugular lymph nodes and in the upper area of the right lobe. The surgeon then performed radical neck dissection on the right side, and a well-differentiated carcinoma was found. Since he could not find the remaining remnant of the right lobe, demonstrated in figure 5c, the attempted total surgical thyroidectomy was completed by a treatment dose of radioiodine. Total ablation of functioning thyroid tissue resulted, as shown in figure 5d.

4. Detection of Pulmonary Metastases From Thyroid Cancer When Chest Roentgenogram Is Negative

A physician underwent total surgical thyroidectomy for carcinoma of the thyroid gland in 1952. In the spring of 1957 a hard node

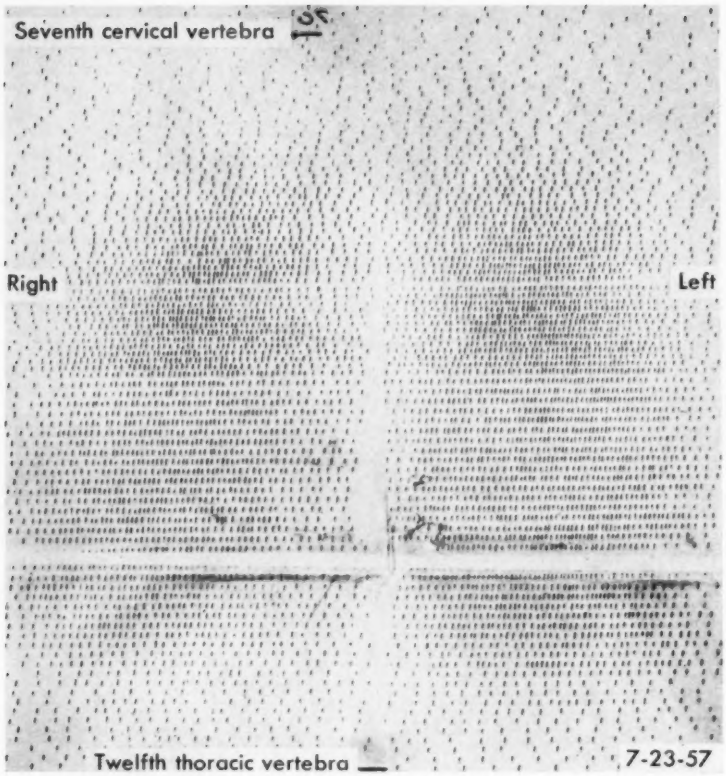


FIGURE 6. Scintiscan showing concentration of I^{131} in miliary metastases throughout both lungs. The chest roentgenogram failed to demonstrate any abnormality.

developed in the right jugular lymph node chain. He was taking 3 gr. of desiccated thyroid per day. Biopsy of the node demonstrated carcinoma from the thyroid gland. When the administration of desiccated thyroid was discontinued for six weeks, no symptoms, signs or laboratory findings compatible with clinical hypothyroidism developed. Physical examination, scintiscanning of the neck, and a thoracic roentgenogram failed to demonstrate evidence of the presence of thyroid tissue, benign or malignant. Since the patient was euthyroid, we knew he must have functioning thyroid carcinoma somewhere, most probably in the lungs. Figure 6 is a scintiscan of the chest. Both lungs appear to be completely infiltrated with functioning metastases of thyroid carcinoma. Localization counting over the chest and abdomen demonstrated that the chest contained approximately four times as much I^{131} as did the abdomen. The patient also excreted less I^{131} in the urine over a 72 hour period than do persons without functioning thyroid tissue. These findings, plus the development of myxedema following two large treatment doses of I^{131} over a period of six months, added further evidence that thyroid carcinoma was present in the lungs.

5. Determination of Plasma and Total Blood Volumes in "Anemia"

When a physician finds that a patient has a subnormal red blood cell count, hematocrit reading or hemoglobin value, he concludes that the patient is "anemic." He assumes that "anemia" means that the total mass of circulating red blood cells is decreased. In reality it may appear to be decreased because of (1) a decreased mass of circulating red blood cells, (2) an increased mass of circulating

FIGURE 7. Scintillation detector (on bench) has a "well." Blood sample in test tube is counted in this well.

plasma, or (3) a combination of the first two factors. The conventional red blood cell count, hemoglobin and hematocrit determinations, and use of Evans blue dye all give relative values and therefore do not define the cause of the apparent anemia.

If the plasma is labeled with radioiodine-labeled human serum albumin and the red blood cells are labeled with Cr^{51}, an absolute hematocrit reading may be obtained and the total volume of plasma and red blood cell mass accurately determined. Figure 7 illustrates the well-type counter and scaler used in counting these specimens.

TABLE 1

PLASMA VOLUME AND TOTAL CIRCULATING RED BLOOD CELL MASS IN HYPERTENSIVE HEART DISEASE*

	ESTIMATED (MILLILITERS)	DETERMINED (MILLILITERS)
Plasma volume	2,475	5,071
Total red blood cell mass	2,025	3,275
Total blood volume	4,500	8,346

*Patient C. G., congestive heart-failure from hypertensive heart disease; 5 ft. 3 in., 230 lb. Hematocrit reading 46 per cent. The marked increase in plasma volume and total circulating red blood cell mass determined with the use of I^{131}-labeled human serum albumin and Cr^{51}-labeled red blood cells could not be predicted in this case by use of the hematocrit.

The body responds to acute loss of blood by replacing blood volume with the most readily available material, plasma. The replacement is overdone so that the anemic patient usually has a supernormal plasma volume and not infrequently a supernormal blood volume. Under such circumstances the use of whole blood for replacement not only is unnecessary but may be fatal in a patient with heart disease; packed red cells are the replacement of choice.

Table 1 demonstrates the marked increase in plasma volume and total circulating red blood cell mass as determined by means of I^{131}-labeled human serum albumin and Cr^{51}-

TABLE 2

PLASMA VOLUME AND TOTAL CIRCULATING RED BLOOD CELL MASS IN CIRRHOSIS OF THE LIVER*

	ESTIMATED (MILLILITERS)	DETERMINED (MILLILITERS)
Plasma volume	2,113	3,281
Total red blood cell mass	1,445	975
Total blood volume	3,558	4,256

*Patient B. B., 5 ft. 2 in., 106 lb. Hematocrit reading 31.9 per cent. The low hematocrit, caused in part by the decrease in total red blood cell mass, was accentuated by an increase in plasma volume 1 l. above "normal." Because of the resultant increase in blood volume, packed red blood cells are the replacement of choice.

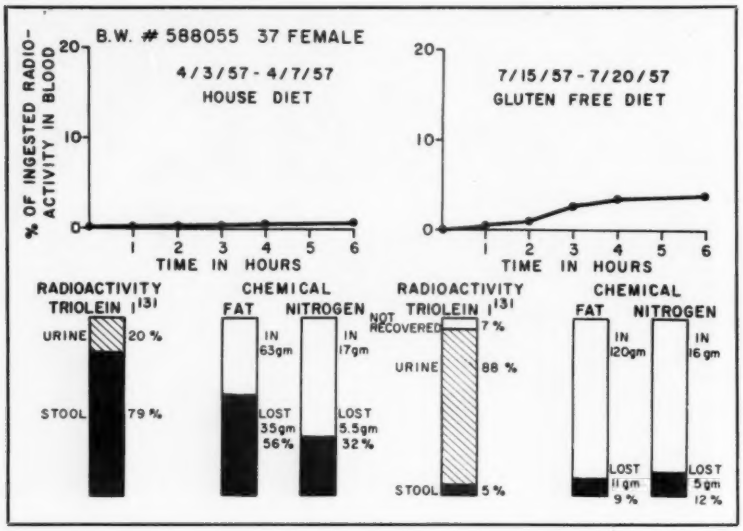


FIGURE 8. Malabsorption defect in nontropical sprue demonstrated by studies utilizing I^{131}-labeled fat before and after treatment with gluten-free diet. These results compare favorably with conventional quantitative chemical balance studies.

(Courtesy of Dr. A. French.)

labeled red blood cells compared with the estimated values in a patient with congestive heart-failure from hypertensive heart disease whose hematocrit reading was normal. Table 2 shows how the total blood volume may be elevated due to increased plasma volume in an "anemic" patient with cirrhosis of the liver. Although the low hematocrit reading in this patient was caused in part by the decrease in total circulating red blood cell mass, it was accentuated by an increase in plasma volume above "normal." A similar picture in a case of low-grade bleeding from a duodenal ulcer is represented in table 3, except that the total blood volume is "normal."

TABLE 3

PLASMA VOLUME AND TOTAL CIRCULATING RED BLOOD CELL MASS IN BLEEDING DUODENAL ULCER*

	ESTIMATED (MILLILITERS)	DETERMINED (MILLILITERS)
Plasma volume	2,748	3,878
Total red blood cell mass	2,080	817
Total blood volume	4,828	4,695

*Patient H. B. Hematocrit reading 28.2 per cent. Same changes as shown in table 2 for hepatic cirrhosis are also found in slow bleeding from a duodenal ulcer except that the total blood volume is "normal."

6. Diagnosis and Determination of Cause of Malabsorption Syndrome

When a patient loses weight and has diarrhea, lack of absorption of food from the gastrointestinal tract should be considered as a possible cause of the illness. Conventional inspection of feces for fat droplets and meat fibers is not quantitative. Few hospitals are equipped to perform the relatively laborious conventional quantitative chemical balance studies. Radioiodine-labeled neutral fat (triolein), fatty acid (oleic acid) or both can be utilized more easily to quantitate the degree of malabsorption. Malabsorption of the radioiodine-labeled fat is detectable by an increased excretion of radioiodine in the feces, with a resultant subnormal concentration in the blood and excretion in the urine. Excretion of excessive amounts of labeled oleic acid in the stools indicates that malabsorption exists because of hypermotility of the intestine, disease of the intestinal wall, gastrectomy, or other such factors. If radioiodine-labeled neutral fat appears in excessive quantities in the stool but radioiodine-labeled oleic acid is absorbed properly, the usual cause of the malabsorption syndrome is lack of pancreatic lipase.

Figure 8 shows the presence of malabsorption and the response to treatment with a

FIGURE 9. Instrumentation used in performing head counts and abdominal counts in I^{131}-rose bengal test for differentiation of intrahepatic and extrahepatic obstructive jaundice.

gluten-free diet in a case of nontropical sprue. The results of the counts to determine the radioiodine-labeled triolein in stool, blood and urine are confirmed by simultaneous conventional quantitative chemical balance studies.

7. Differential Diagnosis of Intrahepatic and Extrahepatic Obstructive Jaundice

The clinician still finds it very difficult to distinguish between intrahepatic obstructive jaundice and the extrahepatic type. Rose bengal dye labeled with radioiodine and injected intravenously is a very helpful agent in making this differentiation. Figure 9 illustrates the positioning of the scintillation detector tubes used in counting over the head and small intestine. The rate at which the count over the head declines is correlated with the rate at which the labeled rose bengal is concentrated from the blood by the liver. The abdominal count first falls, reflecting the fall in concentration of levels in the splanchnic blood. The abdominal count then rises if bile is excreted through the biliary duct system and into the small bowel.

Figure 10 shows the curves obtained after intravenous administration of radioiodine-

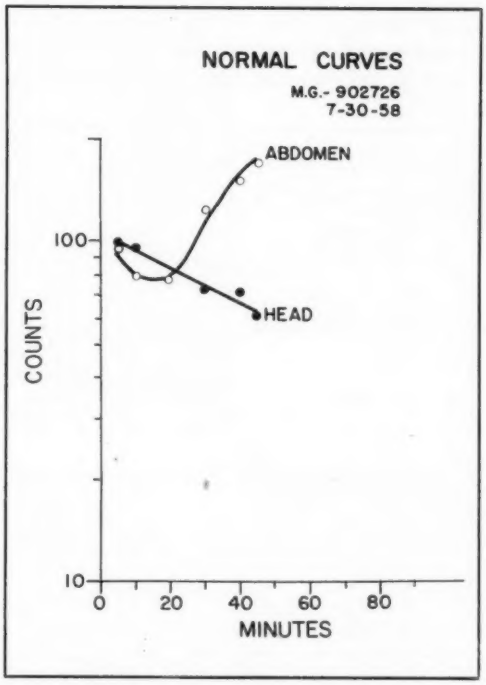


FIGURE 10. Counts over head and abdomen after intravenous injection of I^{131}-rose bengal in patient with normal liver function and no extrahepatic duct obstruction.

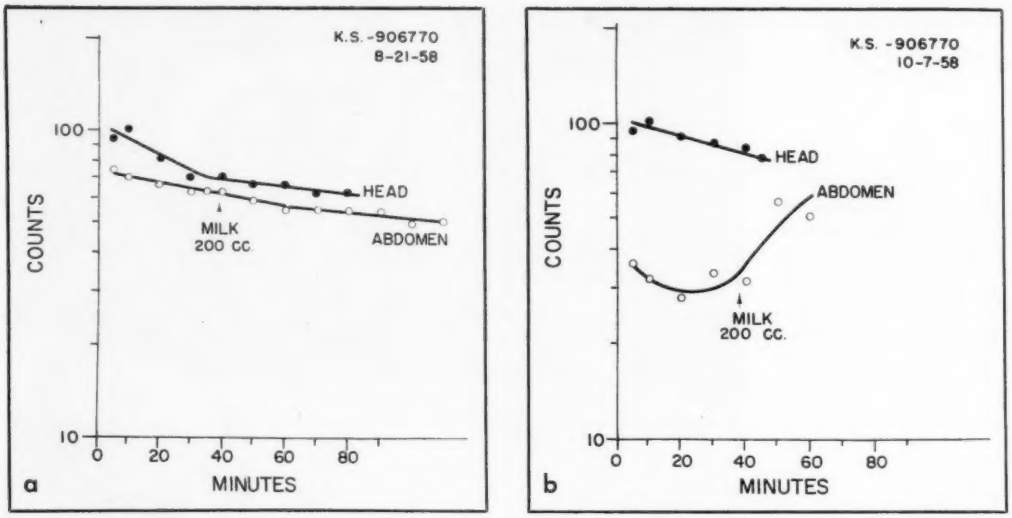


FIGURE 11a. Counts over head and abdomen of a patient with extrahepatic biliary obstruction (stone in the common bile duct) but little if any hepatic insufficiency.
b. Counts over head and abdomen of the same patient after removal of the stone.

labeled rose bengal in a patient without hepatic disease. Figure 11 represents a case of extrahepatic obstructive jaundice caused by a stone in the common duct. Before operation, there is a lack of appearance of the dye in the intestine, but clearance from the blood is normal (figure 11a). After removal of the stone (figure 11b), the labeled rose bengal appears normally in the small bowel.

When the jaundice is of the intrahepatic obstructive type, the blood curve falls at a subnormal rate but some radioiodine-labeled rose bengal does appear in the small bowel (figure 12).

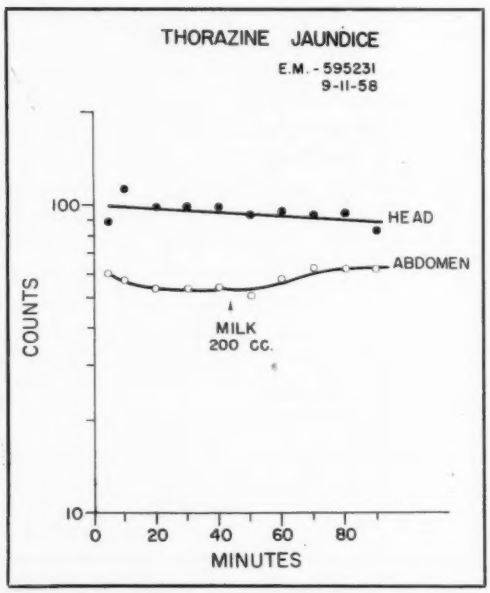


FIGURE 12. Counts over head and abdomen in a patient with intrahepatic obstruction.

8. *Detection of Unilateral Renal Disease*

Many times, intravenous or retrograde pyelography or abdominal aortography is contraindicated or of little value in the diagnosis of renal disease. Radioiodine-labeled DIODRAST® may be a helpful diagnostic aid, particularly in finding unilateral renal disease in these circumstances. Scintillation detectors over the renal areas, in circuit with rate meters and recorders (figure 13), time and compare the relative amount of labeled Diodrast brought to the kidney by the blood, filtered by the glomeruli, and excreted into the collecting system. The recordings obtained by this method in a patient with normal kidneys are shown in figure 14. Figure 15 shows the difference

FIGURE 13. Two scintillation counters pointed over the kidneys in the performance of I^{131}-labeled Diodrast studies of comparative renal function.

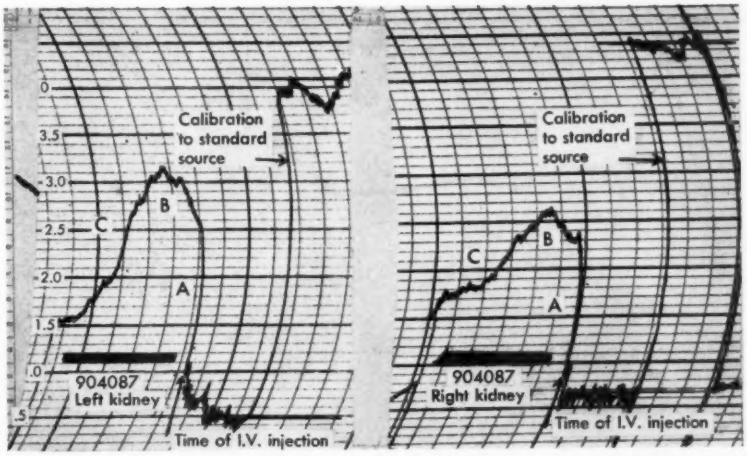


FIGURE 14. Graphic recording of the pattern of rise and fall in radioactivity from I^{131} over the kidneys in a patient with normal renal function.

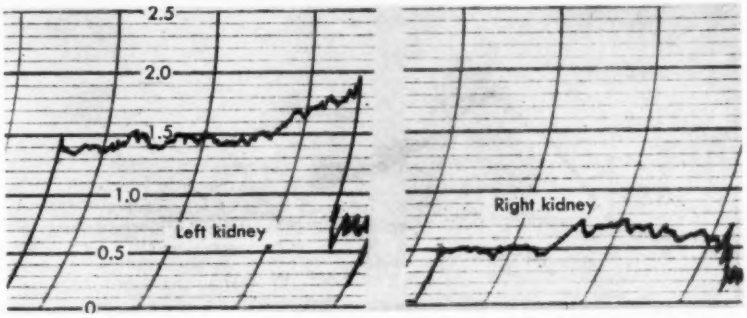


FIGURE 15. Markedly decreased radioactivity count rate over the right kidney in a case of chronic atrophic pyelonephritis of the right kidney, proved surgically, and necrotizing vasculitis (poor function, left).

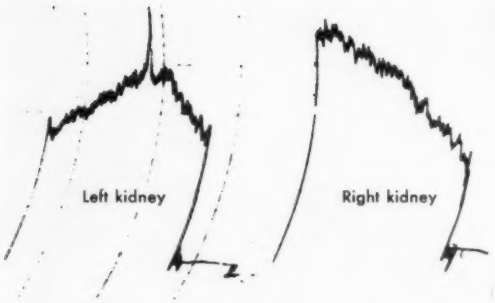


FIGURE 16. Slowed renal excretion of I^{131}-Diodrast from right kidney because of ureteral obstruction.

in curves produced by atrophic pyelonephritis in the right kidney. A similar picture was found in a patient who had coarctation of the renal artery. The decrease in height of the tracing from the diseased kidney is caused principally by lack of normal renal vasculature. Figure 16 depicts a lack of excretory fall in radioiodine-labeled Diodrast counting activity over the kidney of a patient who had obstruction to excretory flow of urine from that kidney because of a stone in the ureter.

9. Diagnosis of Pernicious Anemia When Patient Has Been Treated

If pernicious anemia is suspected and the patient has been treated with vitamin B_{12} sufficiently to normalize the morphology of the marrow and peripheral blood, it is very difficult to substantiate the diagnostic impression. Even in the treated state, the patient with pernicious anemia absorbs orally administered vitamin B_{12} subnormally from the intestine unless supplementary intrinsic factor is supplied. If the vitamin B_{12} cobalt atom is replaced with radioactive cobalt (Co^{60}), the lack of absorption of the labeled vitamin can, under certain standardized conditions, be de-

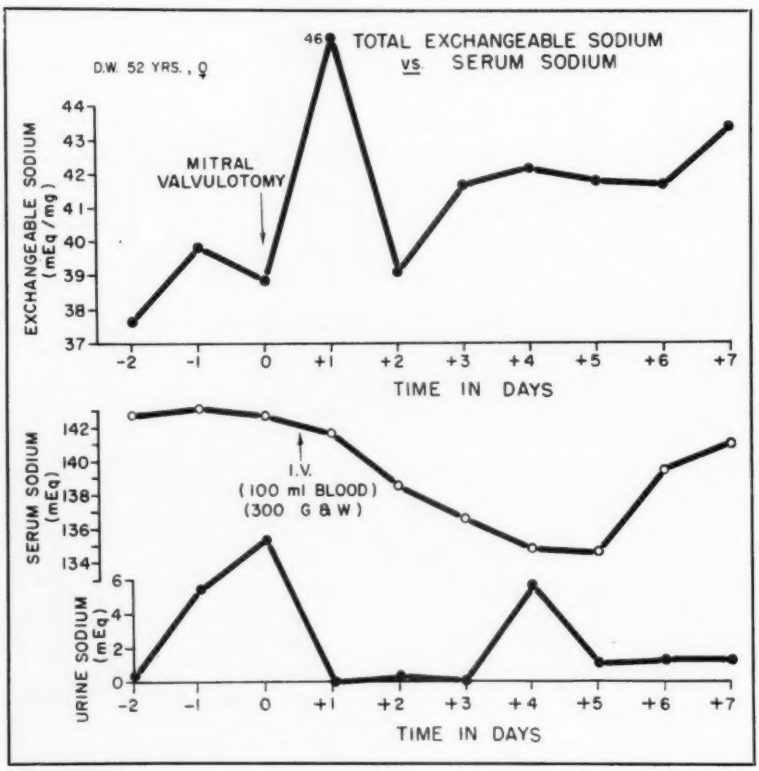


FIGURE 17. After mitral valvulotomy the total exchangeable sodium in the body increases while the serum sodium concentration decreases.

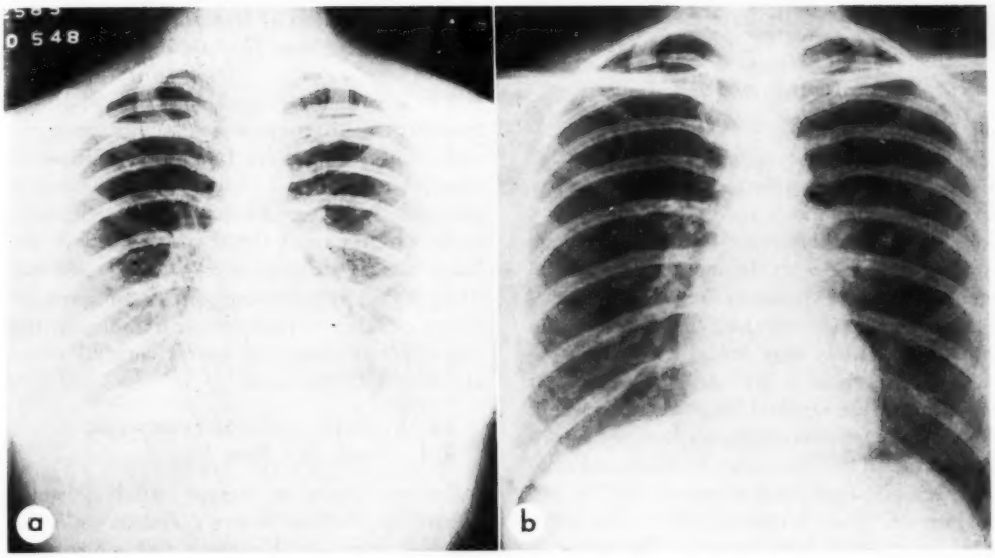


FIGURE 18a. Functioning carcinoma of the thyroid gland metastatic to the lung, before I^{131} therapy.
b. Relatively normal chest roentgenogram after successful I^{131} treatment.

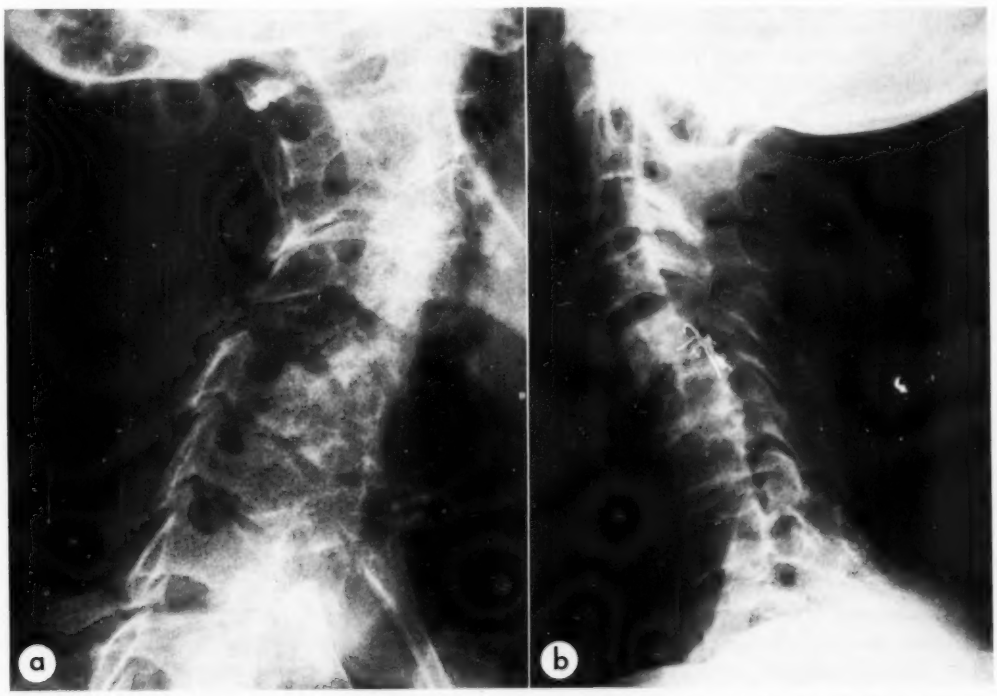


FIGURE 19a. Functioning carcinoma of the thyroid gland metastatic to the fourth cervical vertebra, before treatment with I^{131}.
b. Roentgenogram of cervical spine after apparently successful treatment with I^{131}.

tected relatively easily by subnormal urinary excretion.

10. Determination of Total Available Body Electrolytes

The conventional chemical determination of serum sodium merely measures the concentration of sodium in a specimen of serum; it does not tell the clinician how much sodium is in the patient's body. In some disease states, such as in the hyponatremic, edematous patient with cardiac disease, the available sodium in the body may actually be increased in the presence of a decreased concentration of sodium in the serum. Using the isotope dilution principle, the available sodium, potassium or chloride in the body may be measured relatively simply. Radioactive sodium (Na^{22}), potassium (K^{42}) or bromine (Br^{82}) (for chloride) is injected intravenously. The urine is collected for 24 hours, and a blood specimen is drawn at the end of the 24 hours. Available electrolytes (total "exchangeable" or "space" determinations) are calculated from the radioactivity in blood and urine. Figure 17 shows the lack of correlation between serum sodium concentration and total exchangeable sodium, as measured with Na^{22}, in the period after mitral valvulotomy.

11. I^{131} in Treatment of Thyroid Disease; Hyperthyroidism After Subtotal Thyroidectomy

The most widely accepted use of I^{131} today in the treatment of hyperthyroidism is for persistent or recurrent thyrotoxicosis after thyroidectomy. The rationale is that the operative morbidity is increased by disturbances of landmarks by the first operation. No morbidity other than a small number of instances of hypothyroidism has been observed from I^{131} treatment of hyperthyroidism over a period of 17 years.

12. Treatment of Metastases to Lung and Bones From Thyroid Carcinoma

I^{131} is commonly used with benefit in the treatment of thyroid cancer after surgery, irradiation or both have failed to eradicate all functioning thyroid carcinoma. The roentgenograms in figure 18 show clearing of metastatic carcinoma of the thyroid gland in the lungs after I^{131} treatment in a 13 year old boy with rapidly progressive disease. Figure 19 shows clearing of metastatic carcinoma of the thyroid gland from the fourth cervical vertebra after I^{131} treatment.

13. Radiophosphorus Treatment of Polycythemia Vera

Conventional x-ray therapy of polycythemia vera often produces severe radiation sickness, requires considerable time and effort, and usually is relatively expensive. Radiophosphorus (P^{32}) injected intravenously goes to bone and suppresses excessive hematopoiesis in this condition. The injection does not require hospitalization and need not be given more often than once every three months.

14. Demonstration of Adequate Blood Supply in Tubed Pedicle Flap

In the past, plastic surgeons had to rely on subjective information to decide when a tubed pedicle flap had sufficient blood supply for it to be "swung" successfully. Now, radioiodine-labeled human serum albumin can be injected into the center of the tube of skin and counts can be made over the flap before and after a tourniquet is removed first from the original end of the flap and then from the transplanted end. When the counting rate falls as rapidly over the transplanted end after removal of the tourniquet as it does over the original end of the flap after removal of the tourniquet, the new vascular supply is adequate.

The Management of Anticoagulant Therapy

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Safe, effective anticoagulant therapy requires observance of certain principles of management. The physician must be certain that an absolute contraindication to such therapy does not exist, must be familiar with the agents employed, and must know how to reverse their effects promptly. He must rely on the laboratory for specific information concerning the effects of the drug on the clotting mechanism, but it is his responsibility to interpret the test results clinically.

HEPARIN and the oral anticoagulant agents are commonly employed in this country and abroad for the treatment and prevention of thrombosis and embolism. There is general agreement on the indications for and contraindications to the use of these drugs, but rather wide differences of opinion exist in regard to the most suitable laboratory method to measure the clotting abnormality produced by treatment.

Safe, effective control of anticoagulant therapy depends on proper selection of patients, comprehensive understanding of the pharmacology and side effects of the anticoagulant employed, knowledge of the antagonists available to control excessive anticoagulant effect when bleeding threatens or occurs, and proper utilization of the laboratory tests available for regulation of treatment.

Selection of Patients

Persons most likely to benefit from anticoagulant therapy during an acute illness are those with myocardial infarction, pulmonary embolism, deep venous thrombosis, arterial embolism not amenable to surgical therapy, retinal arterial or venous thrombosis, and certain forms of intermittent basilar or carotid arterial insufficiency. Anticoagulants should be administered prophylactically to patients for whom bed rest is prescribed if they are predisposed to the development of venous thrombosis and pulmonary embolism by the presence of one or more of the following factors: (1) past history of deep venous thrombosis, (2) leg trauma, (3) extreme obesity, (4) certain malignant neoplasms, and (5) congestive heart-failure. On a long-term outpatient basis this therapy may be of prophylactic value to patients with recurrent or mi-

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gratory deep venous thrombosis, recent or recurrent myocardial infarction, recurrent episodes of pulmonary embolism, recent or remote cerebral vascular accidents, or repeated arterial embolism from an intracardiac site.

It is quite well established that these drugs are of prophylactic value in patients with myocardial infarction and will decrease the mortality rate from recurrent infarction. They are relatively ineffective in modifying or decreasing the frequency of pain in angina pectoris. Similarly there is as yet no conclusive evidence that they are of value in the syndrome of impending myocardial infarction; however, because of the nature of this condition a well-controlled study is difficult to carry out. Until this problem is settled, persons with this clinical picture should receive prompt and adequate anticoagulant therapy.

If an indication for anticoagulant therapy exists, the patient should be evaluated for the presence of serious contraindications to the use of these agents. Definite and absolute contraindications include severe hepatic disease with marked hypoprothrombinemia, severe renal disease, congenital or acquired hemorrhagic disorders, and recent operations on the eye, brain or spinal cord, in which cases a hemorrhagic complication of therapy might prove disastrous. Other, less absolute contraindications include recent operations on the urinary bladder, large open wounds, and the presence or a past history of peptic ulcer or other ulcerative lesions of the gastrointestinal tract. In the latter situations the benefits expected from therapy must be weighed against the possibility that serious hemorrhage may result from the induced hypoprothrombinemia.

Selection of the Anticoagulant

There are two main groups of anticoagulants in general use: heparin and heparinlike substances, and the oral anticoagulants (coumarin and indandione derivatives). The heparinlike substances (dextran, TREBURON® and PARITOL®) are sulfonated polysaccharides and for various reasons are not satisfactory for clinical use. Consequently the only important member of this first group is heparin.

Heparin

The effect of heparin is best measured by the Lee-White whole blood clotting time (table 1). Other tests in use for this purpose are the silicone tube clotting time and the capillary tube clotting time; the former method is exceedingly time-consuming and the latter quite inaccurate, and thus neither technic is as suitable as the Lee-White method. Determinations of "prothrombin activity" have no place in the control of heparin therapy. Although the "prothrombin time" is prolonged when the clotting time is greatly prolonged by heparin, there is no reliable correlation between the two tests. The depression of "prothrombin activ-

TABLE 1

WHOLE BLOOD CLOTTING TIME
(MODIFICATION OF LEE-WHITE METHOD)

CONDITIONS NECESSARY TO ASSURE ACCURACY:

1. Scrupulously clean glassware
2. A "clean" venipuncture of an easily accessible vein (or the use of the two syringe technic)
3. Test tubes of 8 mm. internal diameter
4. Strict adherence to details of technic

TECHNIC:

1. Five milliliters of blood is drawn into a clean, dry syringe through an 18 or 20 gauge needle.
2. The needle is removed from the syringe and exactly 1 ml. of blood is placed in each of two test tubes.
3. Three minutes from the time blood entered the syringe, tilting of the first tube at 30 second intervals is commenced and is continued until the tube can be completely inverted without displacement of the clot.
4. The second tube is then tilted at 30 second intervals until the same end point is reached.
5. The time from the appearance of blood in the syringe to the end point in the second tube is recorded as the clotting time.

NORMAL VALUE: 7½ to 15 minutes

ity" produced by heparin is due in great part to a physical effect of heparin in vitro and has no direct relation to the degree of anticoagulant effect in vivo. Some effect on "prothrombin activity" may be expected, however, when the Lee-White clotting time is longer than 25 minutes.

Heparin is the most rapidly effective, the most predictable and dependable, the most rapidly reversible, and in some ways the most convenient to use of the anticoagulants available for clinical purposes. Unfortunately, an anticoagulant effect is produced only by parenteral administration and it is relatively expensive. The expense is of less concern when this agent is used for the therapy of acute conditions only or as a means to obtain an immediate anticoagulant effect as a preliminary to subsequent therapy with oral anticoagulants. Heparin can be administered intravenously, intramuscularly or subcutaneously.

When heparin is given intravenously, the patient's blood is often incoagulable if tested immediately after the injection. Over the next several hours, however (the exact time depending on the dose administered), the clotting time returns to normal levels (figure 1). The usual amount of heparin administered by this method during any 24 hour period is 300 mg. Suitable dosage schedules are 50 mg. every four hours, 75 mg. every six hours, and 100 mg. every eight hours. Heparin is available in various concentrations; dilute solutions (10 mg. per milliliter) are preferable for intravenous use. More concentrated aqueous solutions frequently produce pain at the site of injection. If heparin is administered by intermittent intravenous injection, the discomfort produced by multiple venipunctures may be obviated by inserting a polyethylene catheter into a superficial vein of the arm through a large-bore needle. The catheter is taped in place, a syringe is attached, and heparin is injected at suitable intervals. With the intermittent intravenous method, only one or two determinations of clotting time need be made. These tests, done just before a scheduled dose of heparin, should give results within the normal range of 7½ to 15 minutes. This precaution is necessary to detect the rare patient who may be unusually sensitive to heparin.

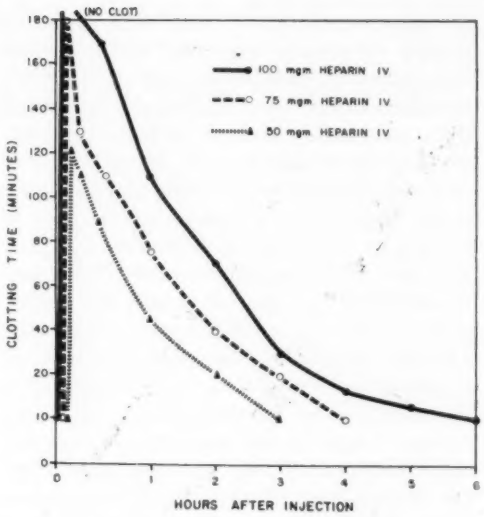

FIGURE 1. Effect of intravenously administered heparin on the clotting time of whole blood.

A continuous intravenous infusion of a dilute solution of heparin provides "fingertip" control of anticoagulant effect, but it is somewhat hazardous and should not be used unless an attendant can observe the exact rate of flow of the infusion from moment to moment. In addition, frequent determinations of the clotting time are necessary to prevent excessive heparin effect.

Heparin also may be administered intramuscularly or subcutaneously. Painful hematomas occur more frequently when it is given intramuscularly. While intravenous injection produces a two to four hour effect on the clotting time, depending on the dose used, the subcutaneous route of administration results in prolongation of the clotting time for 8 to 12 and, in some instances, as long as 18 hours. Accordingly, subcutaneous injections need be given only every 12 hours. The average single dose is 200 mg. with a range for adults of 125 to 300 mg. A disadvantage of this route of administration is that the rate of absorption may vary as additional doses are given and a cumulative effect may result when heparin is absorbed from more than one depot at a time. Also, no matter how carefully the injections

are made, ecchymoses occur with some frequency. Of greater importance is the observation that subcutaneously administered heparin occasionally may have no effect on the clotting time, presumably because of heparin-inhibiting substances present in the tissues. The clotting time should be determined four to six hours after the first subcutaneous dose of heparin to be certain that an effect has been obtained. Subsequently the clotting time must be determined at least once each day, immediately before a scheduled dose of heparin. The next dose can be increased or decreased to adjust the clotting time to the desired level. For subcutaneous administration, aqueous solutions of heparin are available in concentrations of 100 and 200 mg. per milliliter. Ideally, the clotting time 12 hours following injection is maintained between 20 and 30 minutes.

The use of heparin in a slowly absorbed menstruum is unnecessary. These preparations are somewhat unpredictable and apt to cause considerable discomfort and thus are generally less satisfactory than a highly concentrated aqueous solution of heparin.

Heparin given sublingually has no effect on the clotting time. It should be given by this method only for whatever effect it may have on lipid metabolism.

The anticoagulant effect of heparin must be counteracted when a surgical emergency occurs or when serious bleeding is present. Protamine sulfate administered intravenously will accomplish this readily. One milligram effectively reverses the action on the clotting mechanism of 1 mg. of circulating heparin. Accordingly, to counteract the effect of 100 mg. of heparin administered intravenously only a few minutes before, 100 mg. of protamine sulfate in a single intravenous dose will be adequate. If the 100 mg. of heparin had been given two hours before, 50 mg. of protamine sulfate would suffice. Since this antagonist itself, given in excess, can prolong the clotting time, overlarge doses are to be avoided. The Lee-White clotting time will return to normal within one minute after injection of adequate amounts of this antagonist.

When heparin has been administered intramuscularly or subcutaneously, additional absorption from the injection site may take place after the intravenously injected protamine sulfate neutralizes circulating heparin. An ice bag applied over the site of heparin injection will delay further absorption, but additional intravenous doses of protamine may be necessary if "rebound" prolongation of the clotting time is observed. An alternative method is to give an intravenous dose of protamine equal to the estimated amount of circulating heparin and then administer by slow intravenous infusion a dilute solution of protamine sulfate sufficient to neutralize the remaining heparin as it is absorbed from the subcutaneous or intramuscular depot.

Oral Anticoagulants

The term "oral anticoagulants" is used to describe the "prothrombin-depressing" agents and to distinguish them from heparin, which must be given parenterally. While some of the oral anticoagulants may be administered intramuscularly or intravenously, these routes are restricted to patients who cannot take medications by mouth. Parenteral administration does not shorten the latent period (10 to 48 hours) between administration and maximal hypoprothrombinemia.

The many oral anticoagulants suitable for clinical use can be divided into two general types of chemical compounds, the indandiones and the coumarins (table 2). All members of both groups apparently act by depressing the production of at least two clotting factors, factor VII and prothrombin, by the liver (figure 2).

DICUMAROL® was the first of these drugs to be used clinically. It has withstood the test of time by not presenting evidence of long-term toxicity. A fairly long list of other drugs with actions similar to that of Dicumarol have been introduced individually with enthusiasm and claims of superiority. Each in turn, in our experience at least, has proved satisfactory but has offered no distinct advantages or disadvantages compared with Dicumarol, especially when the latter drug is given by a physician who is completely familiar with its use.

There are some minor differences between the various oral anticoagulants (table 3),

TABLE 2

ORAL ANTICOAGULANTS

COMPOUND	TRADE NAME	LOADING DOSE (MILLIGRAMS)	USUAL DAILY MAINTENANCE DOSE (MILLIGRAMS)	INTERVAL TO MAXIMAL EFFECT (HOURS)
Coumarins				
Bishydroxycoumarin	DICUMAROL®	400-700	25-100	48-72
Ethyl biscoumacetate	TROMEXAN®	1800-3000	300-1200	18-30
Cyclocumarol	CUMOPYRAN®	200-400	25-175	24-36
WARFARIN® sodium	COUMADIN® WARCOUMIN® ATHROMBIN®	30-60	3-12.5	48-72
Phenprocoumon	LIQUAMAR® Marcumar	18-30	2-6	48-72
Acenocoumarin	SINTROM®	30-60	2-16	24-36
Indandiones				
Phenindione	HEDULIN® DANILONE® INDON®	400-700	25-200	24-36
Diphenadione	DIPAXIN®	30-60	3-15	60-84
Anisindione	MIRADON®	250-550	25-150	24-36

principally in the time required for maximal depression of prothrombin "activity," but it is our firm conviction that the physician who knows how to use one of these drugs well and who is satisfied with the results should continue in this practice and be skeptical of the claimed but often unconfirmed advantages of newer preparations. Any advantage of one drug over another is based on the factors noted in table 3. These affect chiefly the ease with which a physician can learn to use one of these agents. From this point of view, perhaps the shorter-acting drugs may have some advantage. Duration of action may make one preparation more suitable for acute short-term therapy and another preferable for long-term therapy. It is important to realize that there is no convincing evidence that any one of these drugs is more effective than another as an "antithrombotic" agent. Since these drugs are so similar in most other respects, cost to the patient certainly should be a factor in selection, especially when long-term therapy is contemplated.

The "loading dose" of any of these agents may be given at one time or divided and administered over a two or three day period. In general we prefer the latter method. Treatment of a hospitalized patient with Dicumarol usually is initiated by giving 300 mg. the first day, 200 mg. the second day, 100 mg. the third day, and a maintenance dose of 25 to 100 mg. per day thereafter. The shorter-acting agents, such as phenindione, are administered at 12 hour intervals to provide a more consistent effect over each 24 hour period and to allow easier modification of the dosage schedule. Usually 300 mg. of phenindione is given initially, 200 mg. 12 hours later, 100 to 200 mg. 12 hours later, and 25 to 100 mg. at 12 hour intervals subsequently. Similar dosage schedules may be determined for the other agents, based on the loading dose and on the duration of action of the drug (table 2).

These doses should be used only in patients whose initial "prothrombin activity" is normal (80 to 100 per cent), and *subsequent daily doses should be determined in light of the prothrombin report for each day.* If the initial "prothrombin activity" is low, appropriate reduction in dosage should be made. Certain situations may increase a patient's sensitivity to oral anticoagulants and must be considered when determining the dose. Even if the initial prothrombin concentration is normal, a patient with liver disease or with hepatic congestion due to heart-failure may be unusually sensitive to oral anticoagulants, and the initial dosage should be reduced. This is also true, but to a lesser degree, in patients whose gen-

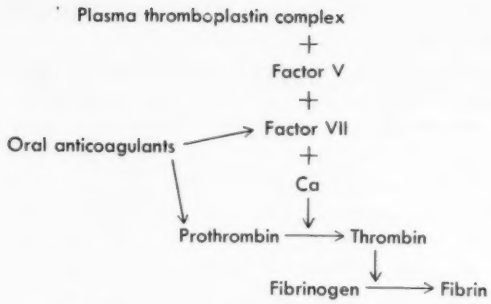

FIGURE 2. Sites of action of oral anticoagulants on the clotting mechanism.

eral nutrition is poor, patients receiving large doses of aspirin, and those who have received broad-spectrum antibiotics orally, as these may largely eradicate the intestinal bacteria responsible for synthesis of vitamin K.

Therapy with oral anticoagulants is best controlled by the use of the Quick one stage test of "prothrombin activity." Many other tests have been proposed for this purpose, and some of these are used regularly in other laboratories. They include two stage prothrombin tests, the Link-Shapiro, Owren, and Ware one stage prothrombin tests, various bedside methods for "prothrombin" determination, and technics for measuring the clotting time of whole blood utilizing capillary glass tubes. We are well aware of the many so-called disadvantages of the Quick one stage "prothrombin" determination but feel that some of these actually may be advantages. For instance, the objection is sometimes raised that this determination measures more than just prothrombin itself. Observations made over the past several years in working with more specialized technics demonstrate very well that not only prothrombin but also factor VII activity in the plasma is depressed by oral anticoagulant therapy. Thus the fact that the Quick one stage test measures the activity of factor VII as well as that of prothrombin seems to be an advantage rather than a disadvantage. This procedure also reflects deficiencies in factor V and fibrinogen and is sensitive to other less common abnormalities of the clotting mechanism. This lack of specificity is not a serious disadvantage.

TABLE 3

COMPARISON OF ORAL ANTICOAGULANTS

Significant differences exist in:

1. Time required for maximal hypoprothrombinemic effect
2. Duration of hypoprothrombinemic effect
3. Amount of available accumulated clinical experience
4. Cost
5. Loading and maintenance doses
6. Availability of dosage forms for parenteral administration
7. Urochromogenic effect
8. Uricosuric effect
9. Chemical structure

Significant differences probably do not exist in:

1. Antithrombotic effectiveness
2. Frequency of hemorrhagic complications of therapy
3. True toxic effects (side effects or toxic effects other than bleeding)
4. Ease with which drugs can be used clinically
5. Effect on clotting mechanism

In our experience the Quick one stage test has been quite satisfactory from the standpoint of technical ease of performance. In addition it provides a safe, reliable index of the effectiveness of anticoagulant therapy. We have not been impressed that capillary tube clotting times or the bedside prothrombin technics offer any real advantage or convenience to the technician. In our hands at least, both of these methods have thus far shown such wide variability that they are practically useless for routine control of anticoagulant therapy. The other tests may substitute very well for the Quick test, but they offer no special advantage and would seem unnecessary in a laboratory where the Quick test is performed satisfactorily.

It is imperative to use the same test to follow anticoagulant effects in a given patient from day to day. Switching back and forth from test to test is improper, as the results in terms of "prothrombin activity" may be quite variable. As an example, we have found that "prothrombin activity" in the range from 10 to 30 per cent by the Owren or Ware technic corresponds very well with "prothrombin activity" of 40 to 60 per cent by the Quick one stage test (table 4).

The physician should be cognizant of the technical aspects of the Quick one stage "pro-

TABLE 4

COMPARISON OF PROTHROMBIN "ACTIVITY" VALUES OBTAINED BY DIFFERENT METHODS*

OWREN METHOD	WARE MODIFICATION OF OWREN METHOD	QUICK METHOD
<10%-16%	<10%-14%	30%-40%
12%-25%	10%-20%	40%-50%
20%-38%	12%-30%	50%-60%

*Determinations performed on plasma samples from patients receiving oral anticoagulants.

thrombin" test as it is performed in his laboratory. A trip to the laboratory and a personal discussion with the technician performing the test are advisable. Knowledge of the exact method by which the results are reported is essential. The most common procedure involves the determination of the "prothrombin" time of a sample of pooled plasma from five normal persons or of a commercially available normal plasma standard. The time is determined from the instant of addition of a mixture of thromboplastin and calcium to the decalcified plasma until a clot forms. This is usually between 11 and 13 seconds, although normal values may be considerably higher in some laboratories. A 50 per cent dilution of the standard plasma with 0.9 per cent saline is made, and the "prothrombin" time of an aliquot of this mixture is determined. This value represents 50 per cent "prothrombin activity" of the normal plasma standard. Further dilutions are made to determine the "prothrombin time" at levels of 10 per cent, 20 per cent and 30 per cent "prothrombin activity." Plotting the "prothrombin time" (in seconds) against the corresponding dilutions of normal plasma results in a parabolic curve (figure 3). Such a curve should be constructed daily. From it the technician is able to read the "prothrombin activity" levels represented by the clotting times of plasmas from patients tested that day. By this technic, with a control value of 12.5 seconds, a patient with a "prothrombin activity" of around 20 per cent will have a clotting time of about 25 seconds.

The other method in common use for reporting the results of the "prothrombin" determination is the "prothrombin *index*." Here no curve is constructed; the result is expressed as a percentage obtained by dividing the "prothrombin time" of the normal control by the patient's "prothrombin time" and multiplying by 100. It is clear that for the patient just mentioned a 20 per cent "prothrombin activity" would be reported as 50 per cent by the "prothrombin index" method. The definition of the optimal therapeutic ranges will differ depending on which of these two methods is employed. If one is aware of the meaning of a percentage figure from a given laboratory there will be no problem (table 5). The possibility of error in this regard may be avoided if the laboratory will report the normal "prothrombin time" in seconds, the patient's "prothrombin time" in seconds, and one of the percentage values just described, clearly labeled as "prothrombin *activity*" or "prothrombin *index*."

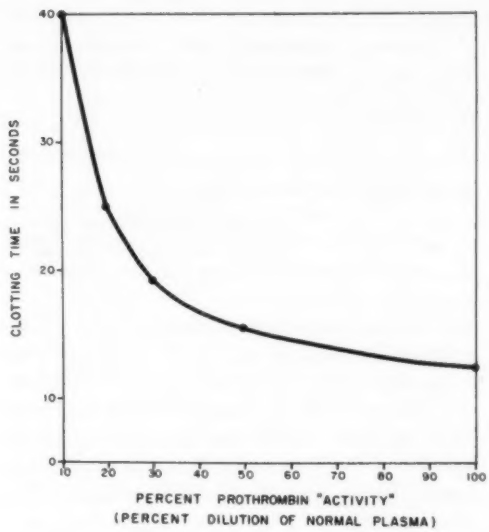

FIGURE 3. Prothrombin "activity" curve used in the Quick one stage test.

Since the introduction of oral anticoagulants in this country, a therapeutic range of 15 to 30 per cent "prothrombin activity" or lower has been considered necessary to affect favorably the course of thrombo-embolic disease. While this may be true, it is interesting to note that the therapeutic range of 10 to 30

TABLE 5

COMPARISON OF PROTHROMBIN "ACTIVITY" AND PROTHROMBIN INDEX WHEN CONTROL PROTHROMBIN TIME IS 12.5 SECONDS AND PATIENT'S PROTHROMBIN TIME IS 25 SECONDS

By reference to the curve constructed from values obtained on various dilutions of normal plasma (figure 3),

25 seconds represents 20% prothrombin *"activity."*

By the prothrombin *index* method,

$$\frac{\text{control prothrombin time (12.5 seconds)}}{\text{patient's prothrombin time (25 seconds)}} \times 100 = 50\% \text{ prothrombin } \textit{index}.$$

per cent as measured by the Owren or Ware technic is the same as the 40 to 60 per cent range by the Quick one stage test (table 4). This means that by the Quick one stage criteria, patients whose therapy is governed by results of the Owren or Ware procedure are hardly being treated at all. Therefore, either they should have an exceedingly high incidence of recurrent thrombosis and embolism or the range as advocated up to the present time for use in hospitalized patients has been unnecessarily low. Support for the latter hypothesis is provided by the fact that most clinics use a Quick "prothrombin activity" range of 30 to 50 per cent for ambulant outpatients receiving therapy with hypoprothrombinemic agents. In these patients, convincing figures have been reported attesting to the value of this type of therapy in preventing or modifying recurrent myocardial infarction.

Vitamin K_1 (MEPHYTON®, KONAKION®) is a specific antagonist to prothrombin-depressing and factor VII-depressing effects of oral anticoagulants. Changes in "prothrombin activity" as measured by the Quick test occur within two to four hours after administration of vitamin K_1. The maximal effect is observed somewhat later than this. In the event of minor bleeding without extreme hypoprothrombinemia (less than 10 per cent) the use of an antagonist usually is unnecessary. Worrisome hypoprothrombinemia (below 10 per cent) can be corrected, when continuation of therapy is desirable, by the use of 1 to 5 mg. of vitamin K_1 given intravenously or by mouth. Moderate bleeding usually requires 10 to 25 mg. of vitamin K_1 given intravenously. The smallest dose consistent with the urgency of the problem should be used if continuation of therapy is planned. A larger dose should be given if treatment is to be terminated. Instances of major bleeding require transfusion of blood and other measures commonly employed for management of hemorrhage and shock. In addition, a dose of 50 to 100 mg. of vitamin K_1 should be given intravenously immediately and repeated once if necessary. There is no significant advantage in the use of fresh blood in this emergency, and stored bank blood usually is employed.

The effects of vitamin K_1 are variable and unpredictable when the drug is given intramuscularly. It has no effect on the prolonged clotting time resulting from administration of heparin.

Long-term Therapy of Outpatients With Oral Anticoagulants

Satisfactory control of long-term therapy depends not only on a conscientious, well-informed physician but also on a dependable laboratory and a reliable patient. This type of therapy is of benefit from the prophylactic standpoint in the prevention of recurrent myocardial infarction, recurrent cerebral vascular thrombosis, and recurrent arterial embolism from an intracardiac source.

The preferred range of "prothrombin activity" for outpatients is between 30 and 50 per cent. The maintenance dose of the oral anticoagulant employed usually is established while the patient is hospitalized. Further adjustments are made on the basis of "prothrombin" tests performed two or three times a week immediately after the patient is dismissed from the hospital and then at longer intervals of two, three and finally four weeks. It is hazardous to maintain patients on anti-

coagulant therapy unless the "prothrombin activity" can be determined at least once each month and more often when necessary.

These patients are encouraged to lead a normal life and usually do so. Treatment is continued for an indefinite period unless contraindications appear. Evidence is accumulating to indicate that, at least in patients with myocardial infarction, maximal benefit is apt to be achieved in patients less than 60 years of age and in the first year following a myocardial infarction.

Hemorrhage

Some hemorrhagic complications are observed in any series of patients treated effectively with heparin or the oral anticoagulants. Bleeding occurs less commonly with heparin than with the oral agents. In our experience the incidence of hemorrhage is about 10 per cent for all patients treated with oral anticoagulants, but in the majority of instances the bleeding is minor. Minor hemorrhage includes epistaxis, easy bruising, more than the usual amount of bleeding after brushing the teeth, prolonged bleeding after nicks during shaving or with other minor cuts, and microscopic hematuria. Major hemorrhage is defined as hematemesis, melena, cerebrovascular hemorrhage, severe bleeding from a wound, massive hematuria, etc.

The possibility of bleeding contraindicates the use of oral anticoagulants in patients who have recently had operations on the central nervous system or eye, and often after urologic procedures, but these drugs usually can be given immediately following other types of operations when the surgeon considers hemostasis adequate. The hemoptysis associated with pulmonary embolism is not considered a contraindication to anticoagulant therapy, and treatment has not resulted in more severe bleeding. In a few cases, gastrointestinal bleeding during anticoagulant therapy has led to the diagnosis of a previously unsuspected peptic ulcer or neoplasm of the gastrointestinal tract. The administration of the oral anticoagulants is not recommended as a diagnostic test for these conditions, however.

When bleeding occurs, conventional methods of treatment often are successful but these should be supplemented by the use of the anticoagulant antagonists already mentioned. Often neglected in discussions of bleeding associated with anticoagulant therapy is the fact that between 2 and 5 per cent of patients on a general medical ward who are not receiving anticoagulants will have bleeding manifestations of one type or another.

Orange-red chromaturia often occurs during phenindione therapy (and to a lesser extent with anisindione) and must not be confused with hematuria. In the latter situation the urine is cloudy or "smoky"; in the former it is perfectly clear even though deeply colored.

Summary

Anticoagulants, both heparin and the orally administered preparations, can be employed effectively *and* safely when certain principles of management are followed. Patients should be selected for good reason, and the physician must be certain that an absolute contraindication to therapy does not exist. He must be familiar with the agents employed and must know how to reverse the anticoagulant effect promptly when necessary. He must rely on the laboratory to provide specific information concerning the effects of the drug on the clotting mechanism, but his is the final responsibility for clinical interpretation of the test results. It is his duty to be fully informed as to the technical methods, the manner of reporting results, and the normal variations of the test employed. He must feel that the test is carefully done and that the results are reliable. When long-term outpatient therapy is to be employed, dependability on the part of the patient is essential and he must be fully informed of the prophylactic nature of the treatment and its potential hazard.

When these conditions are met, anticoagulant drugs may be used as a safe and effective means of preventing thrombosis and embolism.

Postgraduate Medical Education at The University of Michigan Medical Center

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The University of Michigan Medical Center, Ann Arbor

Postgraduate medical education has developed rapidly since World War II due to physicians' demands for refresher courses and graduate training in the specialties.
Postgraduate training at The University of Michigan Medical Center operates under academic direction as a department of the undergraduate medical school, and it is sufficiently decentralized to be within the reach of every practitioner in the state.
The current postgraduate medical program in Michigan includes extramural and intramural courses, affiliated hospital and visiting programs, and training in basic science and general practice.

JOHN M. SHELDON

POSTGRADUATE medical education is of comparatively recent development in the United States. Prior to the turn of the century, young physicians interested in further medical education were forced to go to one of the Old World medical centers such as Paris, London, Berlin, Vienna and Edinburgh.

With an increased demand from practicing physicians for further education to keep abreast of the rapid advances in medicine, an attempt was made to develop postgraduate medical education in the United States. In 1907, the American Medical Association, after a survey of the needs, initiated a program of continuing education through the county societies.[1] For a time, these courses were popular and well supported. Interest, however, gradually diminished; one society after another abandoned the program, and the effort was finally discontinued.

During the next 30 years many medical schools, local societies and other groups developed and sponsored review and refresher courses. Most of these programs were successful for a time, but interest gradually waned and the courses were dropped. A few programs, however, have had sustained interest and have continued to the present time.

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Following World War II, there was a tremendous interest on the part of returning physicians in refresher courses and graduate training in the specialties. With this impetus and the great demand, many medical schools and hospitals developed postgraduate courses as well as an expanded residency program. The interest in postgraduate medical education has continued with the rapid medical advances and with the stimulus provided by the fact that the Academy of General Practice and other groups require their members to maintain a continuing interest in postgraduate medical education.

Development of Postgraduate Education in Michigan

In 1893, the Board of Regents of the University of Michigan authorized the faculty of the medical school to admit medical graduates to one or more of the undergraduate courses. In addition, several new and independent courses were offered to graduates. These courses included hygiene, bacteriology, electrotherapy, microscopic and gross pathology, physiology, histology, chemistry and therapeutics. The courses were presented once a year in the summer and were usually six weeks in length. This program continued with some interruptions until 1920, when it was discontinued.

In 1922, the Michigan State Medical Society inaugurated postgraduate conferences consisting of one or two days of teaching once or twice a year in the 16 councilor districts of the state. Although this program had good attendance and sustained interest, it became apparent that there was a growing need for a type of instruction that included greater continuity and more academic direction.

In 1926, representatives of the University of Michigan Medical School and of the Detroit College of Medicine and Surgery (now Wayne State University College of Medicine) were invited to meet with the council of the state medical society to consider ways and means of providing for the increasing needs for postgraduate education in Michigan. A committee, representing the two medical schools and the state medical society, was appointed to study the problem. In their report the following year, the committee stated that postgraduate education under academic direction was clearly called for and that the University of Michigan as a state tax-supported institution engaged in undergraduate medical education had a particular obligation to undertake such a program, which, after all, was but a continuance of its undergraduate teaching designed to supply competent medical service to the people of the state.

The chief recommendations of the committee were as follows:

1. Postgraduate teaching should not be confined to the University of Michigan Medical School and Hospital, but should be established in many centers throughout the state.

2. In administering the program, the University should seek and maintain the closest cooperation with those extramural centers, with a view toward developing and utilizing existing facilities to the fullest extent.

3. Physicians interested in medical education and qualified to teach should be invited to become extramural members of the faculty.

4. At least in the beginning, rather than instituting a new and separate organization or school, a department of postgraduate medicine should be established within the medical school of the University to direct activities of the program.

In 1927, the board of regents approved the establishment within the medical school of a department of postgraduate medicine, which operated under the usual conditions governing a department of the medical school.[2] At the annual meeting of the state medical society in 1928, the council approved two committees: (1) the Advisory Committee on Postgraduate Education, representing the University of Michigan Medical School, the medical profession, and the state department of health, and (2) a special committee in the city of Detroit (Wayne County Medical Society), where immediate developments were contemplated, to advise on local arrangements.[3]

The program has been developed in accordance with these early recommendations; namely, that postgraduate medical education be carried on under academic direction, that responsibility for it be centered in the under-

graduate medical school, and that it be coordinated but sufficiently decentralized to be within reach of every practitioner of the state.[4,5]

Current Program in Postgraduate Medicine

Extramural courses—The extramural program is a combined project of the Michigan State Medical Society, the Michigan Department of Health, Wayne State University College of Medicine, and the University of Michigan Medical School. Programs are arranged by the department of postgraduate medicine at the University of Michigan, utilizing the faculty members of the two medical schools. Nineteen centers served by this program are located mainly in the rural areas of the state. Teams of two to three faculty members present lectures on prearranged subjects in each center. Where facilities permit and audiences desire, clinical conferences are held. These programs provide a brief postgraduate education experience twice yearly for approximately 800 physicians.[6,7]

Intramural courses—The intramural program provides some 21 refresher courses at the University of Michigan Medical Center. Five of the courses are held one day each week for 16 to 20 weeks. Fifteen courses are of two to five days' duration. The course in the clinical use of radioisotopes is arranged on an individual basis and is usually of four to eight weeks' duration. Although visiting speakers occasionally take part in the intramural courses, the bulk of the teaching is done by the faculty of the University of Michigan Medical School. In 1958 to 1959, about 1200 physicians attended the intramural courses.[6,7] The courses for the years 1959 and 1960 are listed in table 1.

Affiliated hospital program—In the period following World War II, the number of approved residencies in the various specialties was far short of the number of physicians seeking such graduate training. Many hospitals in Michigan had adequate clinical material and a medical staff eager to provide such training. By mutual agreement, an affiliation for residency training was developed between community hospitals and the University of Michigan. The home hospital provided the bulk of the clinical training, but the resident came to the University of Michigan for basic science and also for short periods of residency work in highly specialized areas of medicine available only in a medical center. At the present time, 14 hospitals are in the affiliated hospital program (table 2).

Basic science course—Originally, the basic science course consisted of nine months spent on the University of Michigan campus. Ap-

TABLE 1

POSTGRADUATE COURSES AT THE UNIVERSITY OF MICHIGAN MEDICAL CENTER, 1959-1960

Anatomy (Thursdays), February 11-May 26
Clinical conferences, including all clinical fields (Wednesdays), October 7-March 2
Internal medicine
Electrocardiography and heart diseases (Tuesday evenings), September 8-January 26
Renal, pulmonary and blood diseases (Tuesday evenings), February 2-June 14
Clinical internal medicine (Thursday afternoons), October 1-March 3
Gastroenterology, February 22-24
Rheumatology, March 2-4
Pulmonary diseases, March 14-16
Allergy, March 17-19
Diseases of the heart, March 21-25
Electrocardiographic diagnosis, March 28-April 1
Recent advances in therapeutics, April 4-8
Endocrinology and metabolism, April 11-15
Clinical neurology, April 18-20
Obstetrics and gynecology, January 27-29
Ophthalmology, April 25-27
Otolaryngology, April 21-23
Pediatrics, January 25-27
Psychiatry, February 29-March 1
Diagnostic radiology, April 4-6
Clinical use of radioisotopes, as arranged

TABLE 2

HOSPITALS IN MICHIGAN AFFILIATED WITH THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL FOR RESIDENCY TRAINING

Alexander Blain and St. Joseph Mercy Hospitals, Detroit
Blodgett Memorial, Butterworth and St. Mary's Hospitals, Grand Rapids
Bronson Methodist Hospital, Kalamazoo
Edward W. Sparrow and St. Lawrence Hospitals, Lansing
Hurley and McLaren General Hospitals, Flint
Leila Y. Post Montgomery Hospital, Battle Creek
Pontiac General Hospital, Pontiac
Saginaw General Hospital, Saginaw
St. Joseph's Mercy Hospital, Ann Arbor

TABLE 3

BASIC SCIENCE COURSE, 1959-1960

Pathology, September 28-December 19
Bacteriology, January 4-16
Biophysics, January 18-30
Endocrinology, February 1-13
Biochemistry, February 15-March 5
Physiology, March 7-19
Pharmacology, March 21-26; April 4-10
Anatomy (obstetrics and gynecology), April 11-30
Anatomy (surgery), April-June 3

proximately half of each day was devoted to a review of the basic sciences under the direction of the basic science faculty. The second half of each day was occupied with the clinical correlation and application of the basic sciences. This correlation, under the direction of members of the clinical faculty, was carried out through clinical conferences, lectures, demonstrations and bedside teaching.

With the changing philosophy of some of the specialty boards, the basic science course this year is arranged as a block system. With this change the course can be taken for nine months, or any separate section may be taken alone. Under the block system, in addition to the resident physicians from the affiliated hospitals, a limited number of practicing physicians may attend individual basic science courses (table 3).

Visiting program—The University assists the affiliated hospital by providing a regularly scheduled visiting program by members of the faculty. The purpose of these visits is to aid in the teaching and to evaluate critically the training program in each hospital. Six faculty visits are made annually in the specialty for which the affiliation has been made.

Each member of the faculty visiting the affiliated hospitals is prepared to present a didactic lecture on a prearranged subject in his field of medicine and to conduct a clinical conference on patients presented by members of the house staff. Both the house and attending staffs are urged to be present.

In addition, the faculty representative makes teaching ward rounds with the residents, interns or students and any member of the staff who wishes to attend. After his visit, the faculty representative makes a written report to the chief of the service that he represents and to the coordinator of the program. These reports include his general observations, the number of members of the active and house staffs attending the conference, an evaluation of the degree of their interest and enthusiasm, a report on the general character and quality of patient records, and, especially, his evaluation of the training program.

A one day conference is held at the University once each year for all the education committees of the hospitals, directors of each affiliated hospital, and the chairmen of the clinical departments of the medical school or their representatives. In these conferences, the mutual problems in the over-all programs are considered.

Training in general practice—The postgraduate program in general practice is specifically designed to provide at least two years of training for recent graduates who want to enter general practice. It combines teaching in the environment of a university hospital with the practical approach to common medical problems as they are found in a community hospital. Mercy Hospital, Benton Harbor, and Midland Hospital, Midland, both staffed by practicing physicians representing both the specialties and general practice, are affiliated with this program. To become affiliated, a hospital must possess, in addition to the physical qualifications to meet the requirements of the "Essentials of an Approved Internship," a medical staff that will agree to provide the minimal teaching program outlined in the discussion of residency affiliation.

In an attempt to solve the problem of the distribution of doctors in the less urban communities in the state, hospitals located in rural communities are selected for this program. The University assists these hospitals by selecting from 10 to 12 interns annually; each spends six months of each of the two years at the University Hospital and six months of each of the two years in one of the affiliated hospitals, serving as an intern the first year and as an assistant resident the second. In this manner, each affiliated hospital is furnished with at least two interns and two assistant resi-

dents at all times. The University also provides a teaching resident from the medical and surgical services of the University Hospital on a rotation basis of three months. The teaching resident, in addition to helping with patient care, assists with the organization of the teaching program by planning with the education committee of the affiliated hospital the rotation of interns and residents and the scheduling of ward rounds and conferences, insuring that members of the attending staff meet their scheduled teaching obligations. The teaching resident also shares in the program.

Further assistance is provided the affiliated hospitals by a visiting program in which teams of two faculty members representing the four major specialties visit the hospital nine times each year.

Comment

It can be anticipated that increased numbers of physicians will be attending postgraduate courses. The tempo of medical progress is steadily increasing. American physicians are interested in keeping abreast of the latest progress in order to provide better care for their patients.

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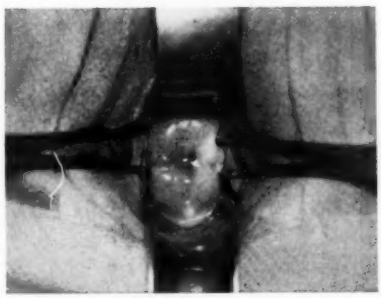
THE UNIVERSITY HOSPITAL, UNIVERSITY OF MICHIGAN MEDICAL CENTER

Scientific Exhibit

Cervical Carcinoma in Situ—the Role of Radical Conization

James S. Krieger and Lawrence J. McCormack

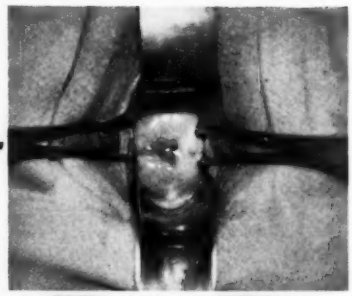
Department of Obstetrics and Gynecology and Department of Anatomic Pathology, Cleveland Clinic, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio



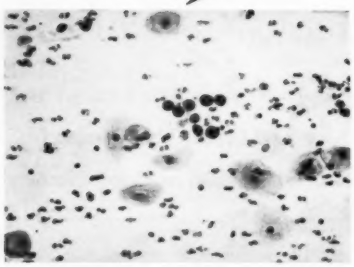
Presented at the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

Detection of Major Cellular Abnormalities

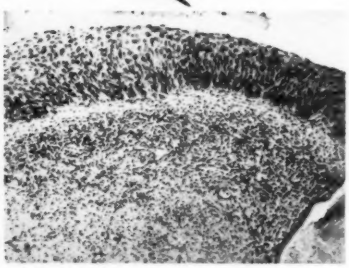
Cytology, Biopsy or Both



Inspection is of little value.



Cytology (positive for atypical cells)



Biopsy (positive for carcinoma *in situ*)

Results of Cervical Cytologic Studies October 1951 to February 1958

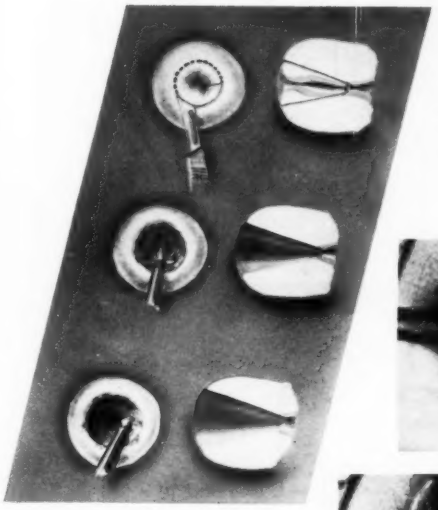
Total specimens	27,637
Invasive carcinoma	130
Carcinoma *in situ*	142
Rate of false negative or false positive results, calculated on total number of histologically proved cases	4 per cent (1 in 25)

Biopsy may establish a diagnosis of carcinoma in situ but does not exclude invasive carcinoma.

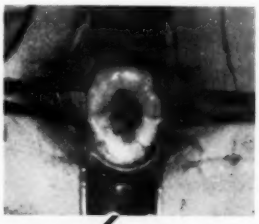
Diagnosis by Radical Conization

Prerequisites

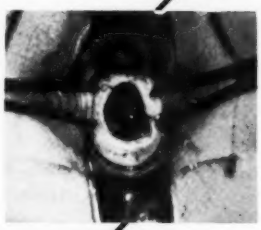
- **Hospitalization**
- **General Anesthesia**

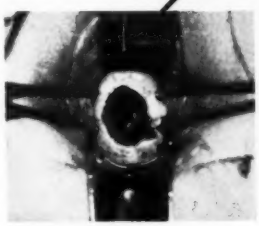


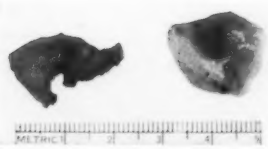
Technic of conization



At operation



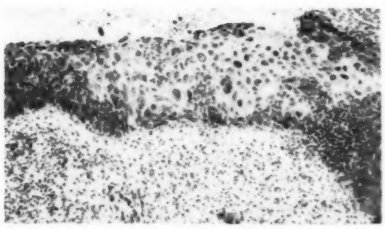




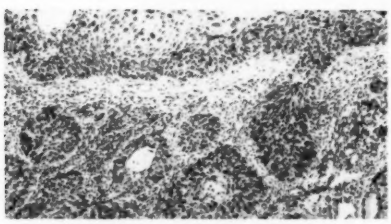
Specimen, knife conization

Preparation of specimen

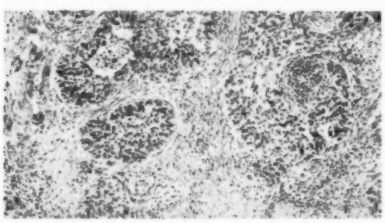
Dysplasia



Carcinoma *in situ*

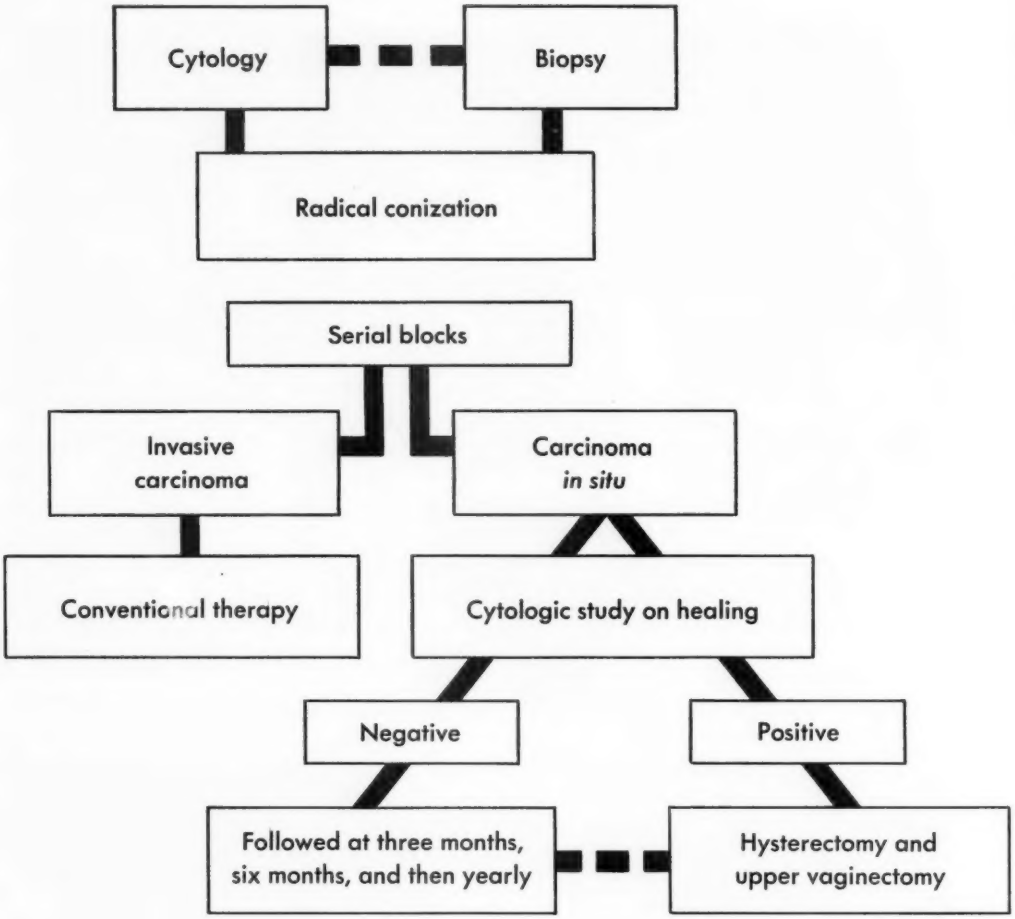


Gland neck involvement



Invasion

A Plan of Therapy



Radical conization may be sufficient for complete therapy if:

- Cervical patency is maintained following conization.
- Cervical cytologic findings revert to normal and remain so after conization.
- No other pelvic pathologic process exists which requires laparotomy.

If these criteria are not met, hysterectomy is indicated.

An Experience With Radical Conization

1950-1958

Total cases treated	124
Radical conization and hysterectomy (or its equivalent)	37
Radical conization	87

Complications of Radical Conization	
Postoperative bleeding delayed (treated with cautery)	0
Stenosis of cervix, primary	6
Vesicovaginal fistula	1

Failure of Radical Conization	
Persistent positive cytology	2
Persistent cervical stenosis	2

Follow-up of Cases Treated With Radical Conization
(Cytologic Study on Cervical Healing at Three Months, at Six Months, and Then Yearly)

	Cases
Less than three years	44
Three to five years	20
More than five years	15
Lost to follow-up	8

A Retrospective Evaluation of Conization

Based on Findings Subsequent to Hysterectomy or Cervicectomy

FINDINGS	NUMBER OF CASES
Specimen negative for carcinoma *in situ*	33
Residual carcinoma *in situ*	
Lesion present in all blocks at conization	1
Multicentric lesion at conization	1
Lesion present in curettings at conization	1
Micro focus in one block in residual specimen	1

Iron-deficiency Anemia in Adolescent Girls

FELIX P. HEALD*

Children's Hospital, Washington, D. C.

IRON-DEFICIENCY anemia is considered by some as one of the more prevalent treatable disorders in medicine. Its classic form in the middle-aged adult is familiar. A similar syndrome of iron deficiency in infancy and early childhood has been adequately described and amply discussed in the medical literature of the last decade. Compared with earlier generations, when chlorosis was common, anemia in adolescence has received scant attention during the last 20 years.

FELIX P. HEALD

In the past, chlorosis was regarded as the prototype of hypochromic anemia in the adolescent girl. Hypochromic anemia in the adolescent differs in several respects from the hypochromic microcytic anemia of middle age. In the adult, achlorhydria is invariably present, as is glossitis. These two findings are usually absent in the adolescent. A classic account of hypochromic anemia in the adolescent was given by Johannes Lange[1] in 1554 ("De Morbo Virgineo"), and in the seventeenth century the efficacy of iron in its treatment was noted. Its existence was widespread and shrouded in mystery. Mention of this disease disappeared from the literature about 20 years ago. Since then, little more has been written about the hypochromic anemia of adolescence. Its disappearance from the medical scene may have been hastened by the decrease in chronic infections, by increased nutritional knowledge, and by the general availability of iron-containing foods to a large number of our population.

That a milder degree of iron deficiency may be present in significant numbers of adolescent girls is evidenced by the unpublished data from the Adolescent Clinic of the Children's Hospital, Boston. These data suggest that such cases with specific clinical findings may go unrecognized. On the other hand, it is

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not uncommon to discover that young girls are being unnecessarily treated with iron supplements on the basis of a "low hemoglobin determination." This superfluous use of iron may be explained by the fact that physicians forget that the normal hemoglobin values of adolescent girls may be lower than those for boys. Judy and Dubach[2] recently reported normal hemoglobin values of 12.61 gm. (mean) with standard deviation ± 0.91. The red blood cell count was found to be 4.37 ± 0.420 cells. Therefore, in the absence of significant findings, a hemoglobin of 11.7 need not be considered abnormal or a sufficient reason in itself for instituting iron therapy.

This poses a difficult problem in clinical medicine, i.e., the detection and treatment of the milder forms of a classic disorder. The less typical are the classic clinical and laboratory findings of a disease, the more critical must be the practicing physician in order to prevent therapeutic abuses. The ensuing discussion will outline principles of diagnosing and treating iron-deficiency anemia in adolescents.

Pathogenesis

Our present knowledge of iron metabolism sheds some light on the pathogenesis of iron deficiency in the adolescent. Much of this information can be obtained from Moore and Dubach's[3] review of iron requirements and metabolism. The amount of iron in the adult is 4 to 5 gm. Table 1 indicates the distribution of iron throughout the body. Deficiency of iron is usually discovered in terms of its effect on hemoglobin production; its effect at the enzymatic and cellular levels is not well understood, yet may well contribute to the symptom complex of iron deficiency. The normal adult diet contains from 12 to 15 mg. of iron per 24 hours. Various nutritional studies indicate that a similar amount of iron is found in the diet of adolescent boys. Adolescent girls' diets contain 1 to 3 mg. less iron than is found in diets of adolescent boys. The absorptive rate for normal subjects is 10 per cent of ingested iron; hence, 1.2 to 1.5 mg. per 24 hours is absorbed. In boys, the normal excretion rates via feces, hair and skin is 1 mg. or less. Thus, a boy on an adequate diet is easily in positive iron balance. In girls, iron loss is compounded by menstrual losses, which are estimated to average an additional 0.5 to 1.0 mg. per 24 hours. Iron losses in girls are precariously close to an equilibrium that is easily converted to a deficit. Figure 1 indicates relative iron balances at various ages for boys and girls.

TABLE 1[4]

DISTRIBUTION OF IRON IN THE BODY

SYSTEM	PER CENT OF IRON
Hemoglobin	60
Myoglobin and cellular enzymes	20
Storage (liver, spleen, bone marrow and reticuloendothelial system in general)	20

Factors such as growth and poor nutrition in adolescent girls create an added demand for available iron. In the first place, blood volume and tissue mass increase during the adolescent growth spurt. Just after the peak of the adolescent growth spurt, with its demands for "growth iron," the first menstrual period occurs, with actual loss of iron from the body. It has been estimated that this loss is in the vicinity of 25 mg. per period.[5] At this crucial point, the emerging woman becomes fully aware of the American obsession for trimness and slimness. Furthermore, these youngsters are unaware that girls physiologically add subcutaneous fat from 12 through 18 years. Frightened at the mere threat of plumpness, the adolescent girl immediately begins the worst sort of regimen, such as Melba toast and lemon juice, at a time when the requirements for nutrients for growth and development are still high. It is small wonder that more nutritional anemias are not detected in this age group. Such a train of events need not be confined to the economically deprived, as vanity resides in all levels of society.

The incidence of anemia in adolescence is unknown. Under conditions of stress during World War II in England,[6] 12 per cent of adolescent girls, 7 per cent of adult women, and less than 1 per cent of adolescent boys and adult men were anemic. Iron deficiency is rare in men, but it may occur in pubescent

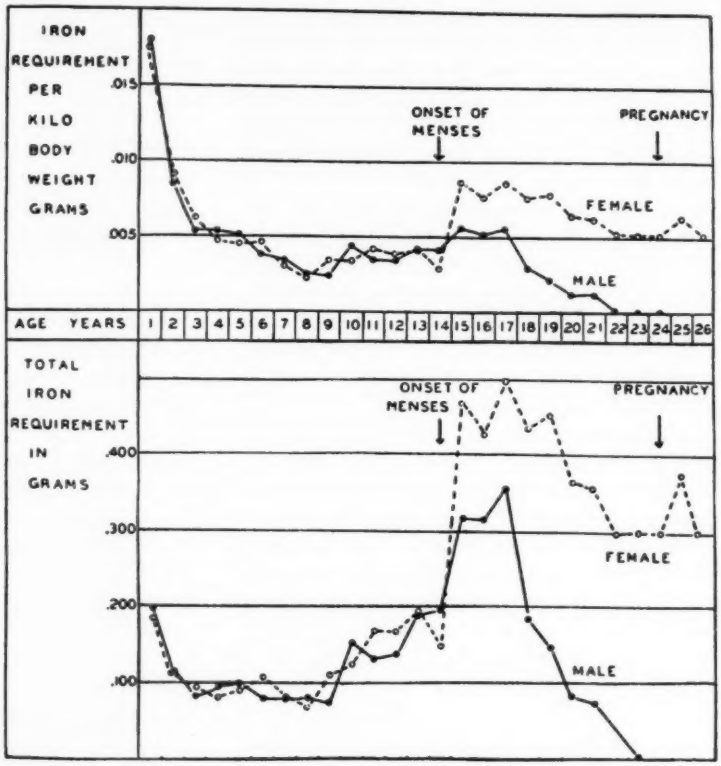

FIGURE 1. Annual iron requirements of children and adolescents. Notice the sharp rise at puberty in girls.

(Reproduced from *Medicine*.[3])

boys. In adolescence, iron deficiency is primarily a disorder of girls.

Diagnosis

It is assumed that all patients with iron deficiency have a hypochromic microcytic anemia. The converse, i.e., an iron-deficiency syndrome without definite evidence of peripheral anemia but with low stores of iron, has received less attention. Recently, Beutler,[7] determining serum iron (low), iron-binding capacity of serum (elevated), and stainable iron in sternal marrow (absent), was able to document milder forms of iron deficiency with relatively normal peripheral red cell cytologic findings. The latter form of iron deficiencies may occur without significant anemia. Even though significant anemia is not present, the symptoms are identical with those of classic iron-deficiency anemia. This may be explained by the fact that iron is concerned with enzymatic and cellular metabolism, so that symptoms may reflect generalized physiologic disturbances rather than just a hemoglobin disorder.

The clinical findings in iron deficiency are consistent from patient to patient. These girls complain of constant headache, fatigue, dyspnea, palpitation, somnolence, loss of energy, and gastric distress. Occasional cramping of the legs is elicited. Previous writings on chlorosis suggested a high incidence of menorrhagia (35 per cent), which often ceased when administration of supplemental iron was started.

Physical examination of these patients may show that the hair is coarse, and it is not unusual to detect cheilosis. One of the more common findings is the change noted in fingernails, in which brittleness, soreness and a tendency to break easily are observed. In addition, the nails are lusterless and may be flat

rather than convex. These abnormalities of the nails are reversed when the deficiency is corrected.

How accurate is original inspection of the mucous membranes and skin in ascertaining the level of anemia in any given patient? McAlpine and Douglas[8] recently reported that on the basis of physical examination, anemia could be detected with reasonable accuracy if the hemoglobin was 9 gm. (60 per cent) or less. As the hemoglobin exceeded 9 gm., accuracy in assessing its correct level proportionately decreased. The most accurate method of clinical assessment was by inspection of the conjunctiva. Thus, physical examination is of less aid in surveying patients for anemia when the hemoglobin is above 9 gm.

In this clinical syndrome, the finding of chronic fatigue or "bone tiredness" is often striking. It is uncommon for adolescents to be chronically fatigued. The opposite condition, being unable to restrain their unlimited energy, usually prevails. Not all youngsters with fatigue have iron deficiency. Psychogenic fatigue and fatigue in postinfection periods are commonly observed. However, the physician must critically search for definitive evidence of iron deficiency before ascribing the symptoms to a neurosis.

Differential diagnosis of anemia in the adolescent is significantly less complicated than in the adult. Anemia secondary to malignancy is uncommon, due to the low incidence of malignancy in the adolescent. Acute leukemia does occur, and anemia with its familiar symptoms may be the presenting complaint; however, this is rare. Chronic bleeding as a source of iron loss must be considered and eliminated. Interestingly enough, young girls with metropathia hemorrhagica during adolescence rarely have clinically detectable iron deficiency. Ulcerative colitis in adolescence is frequently accompanied by iron deficiency and low serum iron values. Aplastic anemia with its pandepression of peripheral cellular elements in the blood presents no problem in diagnosis. Myxedema may imitate or have hypochromic anemia as part of its complex. The anemias with abnormal hemoglobins, such as the sickle-cell or Mediterranean types, are sufficiently characteristic that they are not confused with iron deficiency.

As iron deficiency increases in severity, the more typical are the changes in the peripheral blood. The red blood cell count usually is four million or above and therefore in normal range. In mild iron deficiency, the hemoglobin may be 10 to 12 gm., but as the deficiency increases the hemoglobin falls to levels of 6 to 7 gm. As the hemoglobin falls and the number of red cells remains the same, less hemoglobin is found in each cell, with the consequent pallor gradients. Reticulocytes are usually normal, as is the differential white blood cell count.

A serum iron determination is an unusually sensitive procedure. It must be pointed out that this test measures transport iron, not storage iron. Any event that depresses transport iron will be reflected in its values. Although the serum iron is a sensitive index of iron deficiency, it is also depressed by infection. This dilemma is resolved by determining storage iron in the bone marrow. In iron-deficient patients, no storage iron is present on the marrow smear. With infection, storage iron is either normal or increased. Therefore, if a serum iron value is low, infection must be differentiated from the iron-deficiency syndrome. Since a sternal puncture is not a routine procedure, recourse to the history or physical examination may help resolve the laboratory dilemma.

The serum iron determination is readily susceptible to contamination. Rigid precautions should be used in taking the blood sample, and each physician should consult his laboratory for specially prepared syringes and blood containers. Normal values for serum iron are best obtained from the laboratory where the determination is done. The range of normal values is in the vicinity of 70 to 150 μg.

Treatment

Once the clinical and laboratory diagnostic criteria for iron deficiency have been satisfied, treatment with iron preparations should be started. Ferrous salts of iron are utilized most efficiently. Ferrous sulfate (20 per cent

metallic iron) and gluconate (12 per cent metallic iron) are standard preparations, the latter being less likely to produce gastrointestinal irritation. Ferrous salts combined with ascorbic acid are more readily absorbed than is iron alone; therefore, these preparations may be used. The physician is offered in excess of 325 combinations of iron with various other drugs in the 1959 "Physicians' Desk Reference." This array of medications for use in anemias often is bewildering to the physician and expensive for the patient. In pure deficiency, the therapeutic indication is for iron alone. Replacement therapy in the form of ferrous sulfate or gluconate may cost but one cent per day, whereas useless combinations are often expensive.

The effective dosages are in the range of 1.0 to 1.2 gm. per 24 hours. Fortunately, the uptake of iron rises sharply in iron-deficiency anemias, which aids considerably in the replacement of iron. Iron should be taken after meals rather than on an empty stomach. This timing in medication sharply reduces the frequency of gastrointestinal irritation and diarrhea. Symptoms of intolerance can be further reduced by beginning with one-half the calculated daily dose and gradually increasing the amount of iron to the therapeutic level. If symptoms of gastrointestinal irritation occur, the dosage should be reduced and then maintained at the tolerated level. The length of treatment is inevitably linked to the patient's response. Hematologic values may return to normal, yet cessation of medication may result in a clinical relapse. Therefore, it may be necessary to administer iron orally over a prolonged period, the duration depending on the degree of depletion of iron stores.

Intramuscularly and intravenously administered iron preparations are rarely required in iron-deficiency anemias. Injudicious use of these preparations may lead to undesirable sequelae of an acute or chronic nature. All iron preparations must be kept away from young children, as ingestion of sufficient amounts of iron may lead to fatalities.

In true iron deficiency, the response to iron is prompt and dramatic. The reticulocytes rise between the second and tenth days. Subsequently, there is a rise in hemoglobin (if low) and the red blood cell count. Improvement in the serum iron tends to lag behind. The magnitude of the peripheral blood response is directly proportional to the severity of the patient's anemia.

Symptomatic improvement may occur before there is definitive evidence of peripheral blood changes. The physical findings of pallor, brittle nails and coarse hair revert to normal. If there is no response to administration of iron, the physician may be dealing with a disorder other than simple iron deficiency. A thoughtful review of the clinical findings and more specialized diagnostic procedures may be necessary to establish properly the cause of the adolescent's symptoms.

Summary

The iron-deficiency syndrome during adolescence occurs predominantly in girls. Specific symptoms and physical findings may suggest the diagnosis. Its occurrence without classic findings of hypochromic microcytic anemia is suggested. The use and limitations of serum iron as a laboratory aid are discussed. Treatment with a standard, inexpensive iron preparation is suggested.

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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service

Case Report

A 65 year old clerical worker first entered Hines Veterans Administration Hospital on June 5, 1952. He had a history of peripheral edema of three to four months' duration and of nervousness of one year's duration. Treatment with injections of mercurial diuretics just prior to hospitalization had relieved the edema but had caused a dermatitis secondary to the medication.

The patient's history showed that he had had pulmonary tuberculosis while serving in World War I, but this was considered arrested and asymptomatic. In 1918, he had been treated for syphilis; he had had an appendectomy in 1921, and the following year he had had a unilateral orchiectomy for cryptorchism. Two of the patient's brothers had died of carcinoma; the family history was otherwise noncontributory.

Physical examination revealed that the patient was well nourished and well developed; he appeared apprehensive but not acutely ill. Rales and wheezing were noted throughout the entire left lung, but were more marked in the left upper lobe. There were no rales or wheezing in the right lung. The skin over the abdomen was edematous. The ankles and feet showed bilateral 4 plus edema and 2 plus pretibial edema; 1 plus sacral edema also was present. Slight tenderness of the costovertebral angle was noted. Blood pressure on admission was 130/80. An x-ray of the chest revealed evidence of old fibroid and calcific tuberculosis. The x-ray department suggested that the activity of this tuberculous process should be determined by a repeat film and correlation with the clinical laboratory data. Deep S waves in all chest leads of the electrocardiogram were considered to be abnormal, nonspecific and of the type frequently seen in pulmonary disease. Other laboratory data are summarized in table 1.

The patient's hospital course was uneventful. The edema subsided with bed rest; its cause was still undetermined when the patient was discharged on June 28, 1952.

On October 7, 1956, the patient was readmitted to Hines, complaining that for three weeks he had had shortness of breath, dyspnea on exertion, and severe pain in the left calf. Shortly before this hospitalization, he had had pulmonary function studies and other tests at another hospital, where postural drainage and multiple medications had been prescribed. He had lost 15 lb. in the months preceding readmission, and he complained of anorexia.

Physical examination at this time revealed a symmetrical barrel chest. Generalized wheezing with a prolonged expiratory phase was present throughout the chest; there were no

TABLE 1

LABORATORY DATA

TESTS	1952				1956
	6/6	*6/9*	*6/11*	*6/19*	*10/12*
Urinalysis	Negative				Tr. alb.
White blood cells					6
Red blood cells					20
White blood cell count		7700			6900
Red blood cell count (millions)		5.2			4.8
Hemoglobin (grams)		14.5			12.5
Polymorphonuclear leukocytes		72			81
Lymphocytes		26			14
Monocytes		1			
Eosinophils		1			2
Basophils					3
Hematocrit (per cent)		52			
Erythrocyte sedimentation rate		15			
Sputum (direct smear for tuberculosis)		Negative			
Albumin			3.6		
Globulin			3.2		
Bromsulphalein retention (per cent)				9	
Serologic test for syphilis					Negative

rales or dullness. The patient's fingers showed slight clubbing; there was no cyanosis. Two plus pitting edema was present in both legs, but there was no evidence of Homan's sign. The vibratory sense and jerk of the left ankle were diminished. The left testicle was absent. Blood pressure was recorded at 120/70; pulse was 88 and irregular.

A chest x-ray showed evidence of old and extensive bilateral fibroid and calcific tuberculosis with emphysema at the bases and possible cor pulmonale; however, there was no active tuberculosis. On December 21, an upper gastrointestinal series showed deformity of the duodenal bulb, probably due to an old ulcer, but there was no crater. Diverticulosis of the colon was noted.

An electrocardiogram on October 12 showed a P pulmonale wave and fairly frequent ventricular and occasional auricular premature contractions. These observations were considered compatible with chronic pulmonary disease. On November 16, an electrocardiogram showed sinus tachycardia, old premature ventricular systole, the transition zone shifted to the left, and a P pulmonale wave. These findings also are consistent with chronic pulmonary disease.

Five days after the patient was admitted he complained of pain in the left popliteal fossa, and a positive Homan sign developed in his left leg. At this time the pulse rate was 140 and irregular. After he had had a few days of heparin therapy and bed rest with elevation of the leg, the pulse rate dropped to 76 and was regular. On November 8 the patient had frequent premature contractions, and a few days later he complained of pain in his right thigh. He was given sedatives and intravenously administered heparin followed by DICUMAROL®. The pulse rate increased to 150. Shortly afterward, administration of anticoagulants was discontinued, and on December 4 he again complained of pain in the left calf. He received the same treatment as before, and by December 12 he was allowed to engage in more activity. On December 27, he complained of pain in his right thigh and the right leg was slightly swollen. Four days later, phlebitis was noted at the site of a BROMSULPHALEIN® injection in the right elbow.

Early in January 1957, the patient was put on continuous anticoagulant therapy. The pulmonary findings throughout this period were the same as on admission. In February, the patient was digitalized. On February 8, the pulse rate was 130 and there was no peripheral edema. Femoral pulses were normal. One

week later, marked edema was present in both legs; at this time, the apical rate was 90 and the blood pressure was 110/60. By February 27, progressive edema had developed in the lower extremity and there were rales in the lungs. On March 1, intermittent arrhythmia was noted, and eight days later the pulse rate was recorded as between 100 and 104 with frequent extrasystoles. There were decreased breath sounds in the lower two-thirds of the left lung, both anteriorly and posteriorly, and coarse rales were heard. Penicillin was started because of the clinical impression of pneumonia. Two days later, the patient's feet were painful, edematous and cyanotic. Femoral and radial pulses showed a large volume; the dorsalis pedis was not felt. The apical rate at this time was 88. Progressive gangrene of the feet developed and the patient's right arm began to swell. On March 14, he was transferred to the peripheral vascular service. Four days later, the hemoglobin was recorded as 4.5 gm.; the patient was given transfusions on that day and on the following day, receiving a total of three units of blood. The patient died quietly on March 20.

Discussion

DR. MARTIN M. KIRSHEN (clinical professor of medicine, Chicago Medical School): The patient we are discussing was admitted to the hospital with the primary complaint of unexplained peripheral edema. I was particularly interested in the fact that the phenolsulfonphthalein excretion after 15 minutes was only 20 per cent and the Bromsulphalein tests revealed 9 per cent retention. Both values are slightly abnormal. The patient had far-advanced tuberculosis which allegedly had healed; however, the roentgenologist was not able to determine whether the process really had been arrested, and he suggested that further tests be made. We also do not know whether or not the syphilis had been cured. The patient probably had acquired this disease after World War I, and the treatment at that time was not sufficiently effective to arrest it.

Although the edema in this patient disappeared after bed rest, we must ask ourselves what caused it. Why does a relatively healthy man have edema? Had tuberculosis of the kidney developed? There was no evidence of this in the urine, but when edema develops in a patient who has an old healed tuberculous lesion we should consider the possibility of mild amyloidosis. Classic amyloidosis (massive albuminuria and all the symptomatology of enlarged liver and spleen) is not always clinically present. Cases of mild amyloidosis which never had been diagnosed are found at postmortem examination. For example, severe rheumatic arthritis is very often associated with amyloidosis which does not produce massive albuminuria; sometimes, very little albumin is found in the urine. At the Montefiore Hospital in New York, as many as 25 to 50 per cent of the patients with old healed tuberculosis have had amyloidosis. Thus, it is possible that this patient may have had one of those mild subclinical cases of amyloidosis which was not recognized.

Amyloid formerly was believed to be starch, but we know that it is amino sugar and that it is deposited in different tissues. We differentiate between a primary and a secondary amyloidosis. We assume that the amyloidosis is secondary in a patient who has tuberculosis. It is believed that in the primary disease some involved tissue produces abnormal protein derivatives which are taken up by the reticuloendothelial system and lead to the condition known as amyloidosis.

Classic amyloidosis is not difficult to diagnose, but hidden amyloidosis often is very difficult to detect. The Congo red test is not helpful. Electrophoretic study may reveal a definite abnormal peak of alpha globulins, and, if no other cause is evident, one may suspect amyloid disease. We also are told that increased amounts of glucosamine in the blood may indicate the presence of amyloidosis.

It was suspected that this patient had cor pulmonale. The electrocardiograms suggested the presence of this condition, and it would not be surprising to find it in a man who had such severe calcific tuberculosis with fibrosis. The term "cor pulmonale" is applied to a condition of hypertrophy of the right ventricle; rightly, it should be applied to this

state only when it is due to disease of the lung. If the hypertrophy of the right ventricle is due to a disease of the vessel or of the heart itself, I think many pathologists and physiologists agree that it should be called pulmonary hypertension. It is true that in many patients who have pulmonary disease changes in the vasculature may develop and add the burden of the increased hypertension on the right ventricle.

In reviewing the case to this point then, we may accept that at the time of his first admission to Hines this patient previously had had syphilis and that he had old and probably healed tuberculosis and cor pulmonale. The clubbing of the fingers, which was observed when he was readmitted to Hines four years later, is known to occur in cases of cor pulmonale. At readmission, the patient also complained of severe pain in one leg, and he had pitting edema of both legs. A few days later, pain in the left popliteal fossa and a positive Homan sign developed. He had acute thrombophlebitis. In retrospect, it is possible to say that perhaps the pains which he had had before also were due to thrombophlebitis. This disease is not necessarily manifested by redness or conspicuous swelling; sometimes, it is clinically an inconspicuous condition which is manifested suddenly by a pulmonary embolus.

The patient was given heparin intermittently. Sometimes the edema and pain in his leg disappeared, but occasionally it recurred. A review of the protocol shows that each time he had an acute attack of pain his pulse rate increased and became irregular. Fibrillation developed, which can be explained by the assumption that pulmonary emboli had resulted from the thrombophlebitis. These may be designated as so-called silent emboli.

There is no evidence of an increase in the size of the liver or of splenomegaly. At the beginning of his hospitalization, the patient had a normal blood count, but with the occasional spells of pain and swelling in the leg leukocytosis occurred. Evidence of renal insufficiency developed and the urea nitrogen rose; however, we know nothing of the patient's genitourinary system.

We know that this patient had recurrent thrombophlebitis. It formerly was believed that this was a surgical condition; however, we are learning that it is found much more commonly in general medicine than in surgery. We differentiate two types of this condition: (1) phlebothrombosis, which is not associated with an inflammatory process of the vein, and (2) thrombophlebitis, which is a thrombus formation with inflammation of the wall. We formerly believed that thrombophlebitis was not particularly serious because the clot is attached; however, we have learned that this is not true. Even if the thrombus is attached on one side it can tear away and invade the circulation.

The three important etiologic factors in formation of thrombi are as follows:

1. Stasis of a vein. When stasis occurs, there is a possibility of the formation of a thrombus.

2. Local injury, mechanical or toxic, resulting from pressure or infectious processes.

3. Changes in the structure of the blood. The red blood cells may undergo some change which can produce a premature coagulation or a coagulation under different circumstances, or substances in the serum which can support clot formation may change.

Among the clinical conditions which predispose to the development of phlebothrombosis are myocardial infarct and cardiopathies of different origin (cor pulmonale in this case); localized and systemic infections, of which one of the best known is typhus; blood dyscrasias; primary polycythemia, and some types of anemia, such as sickle-cell anemia. Cancer of the lung and cancer of the pancreas also are known to produce recurrent or migrating thrombophlebitis long before any symptoms of the primary disease are present.

If I am so certain that this patient had only thrombophlebitis, how can I explain the development of gangrene? We are taught that thrombi in the veins do not produce gangrene, and until a few years ago, I held this same opinion. However, I read a very interesting article by Haimovici in a 1950 issue of *Circulation* in which he pointed out that in thrombophlebitis which involves one or more larger veins in the leg nothing will happen to the leg.

When the collaterals are involved, edema appears with compression, severe anoxia develops, and the tissue dies; the pulsating artery is found at amputation.

A similar report came from the Mayo Clinic in 1956, and in *Annals of Internal Medicine* in 1952, Abels reported the interesting observation that in about 70 per cent of the cases in which recurrent thrombophlebitis developed and in which Dicumarol or heparin failed to prevent progression there was carcinoma of the lung or pancreas.

In this case, the recurrent attacks of thrombophlebitis which could not be stopped with anticoagulants, together with a probable pulmonary infarct and the development of gangrene, lead me to believe that we are dealing with carcinoma of the body or the tail of the pancreas. It probably was not sufficiently advanced to produce clinical symptoms or x-ray evidence.

What was the cause of this patient's death? He had a progressive retention of nonprotein nitrogen. Was this due to prostatic obstruction with nephrosis? Was it due to amyloid in the kidneys? I do not know. These are merely speculations not supported by evidence; however, they are good possibilities. Nevertheless, the patient did not die from retention of nonprotein nitrogen. During the last weeks of his illness, the hemoglobin was progressively decreasing, finally dropping to 4.5 gm. The man was obviously bleeding, but we do not know whether the bleeding was in the kidneys or in the gastrointestinal tract. I would propose that the bleeding could have been related to the administration of Dicumarol.

In summary, I would say that this patient also had pulmonary tuberculosis, which probably had healed. He possibly had amyloidosis involving not only the kidneys but also perhaps the liver; this was indicated by the Bromsulphalein retention and a nephrosis of undetermined origin.

DR. WILLIAM E. FREDERICK (assistant chief, radiology service): An intravenous pyelogram made on January 3, 1957, showed no abnormality. The stomach appeared normal on December 21, 1956, and the bulb had prominent folds. There was no evidence of ulcer activity. A chest film made on November 2, 1956 showed that the left base contained an area of fairly well-limited emphysema. The left side of the diaphragm was depressed and the left hilus was elevated. There was a large amount of fibrotic and calcific density. The hilar shadow was prominent and the border of the right side of the heart was not well outlined.

To summarize, x-ray studies of this patient showed an extensive fibrotic and calcific density of both lung fields with upward displacement of the left hilus and pulmonary emphysema at the left base. These findings are seen in chronic pulmonary disease and are probably residuals of old chronic pulmonary tuberculosis without evidence of activity. Cor pulmonale should be read into the situation, but I do not believe that it was present. The right hilus showed some increase in size at the lower pole. There was evidence of an old duodenal pathologic condition, and the barium enema studies showed diverticulosis. The intravenous pyelogram was negative.

DR. MYRON E. RUBNITZ (chief, laboratory service): Before reviewing the gross findings at autopsy, I would like to mention that this patient was afebrile throughout his entire hospitalization except for an occasional temperature of 99.8 or 100° F.

At the time of autopsy, the most interesting findings appeared to be in the lung and probably in the liver, because here was the only definite gross evidence of tumor. Unmistakable metastases were present. Where was the site of the primary tumor? The lung which formerly had been the seat of pulmonary tuberculosis was highly suspected as the primary site not only because of the presence of areas of fibrosis and possible tumorlike nodules but also because of the association of bronchogenic carcinoma with tuberculosis, which we have often seen at Hines. However, there was no endobronchial lesion, so bronchogenic carcinoma could not be diagnosed at autopsy. The pancreas showed some induration which resembled that caused by a penetrating duodenal ulcer rather than that of a neoplasm. The duodenal ulcer did not show evidence of recent bleeding, but there was tarry stool in the lower portion of the small

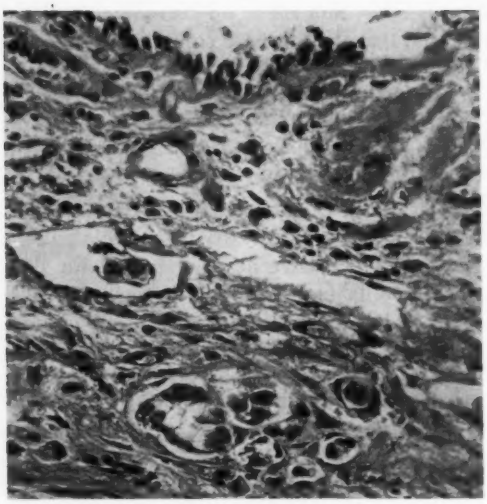


FIGURE 1. Bronchial mucosa with submucosal tumor emboli.

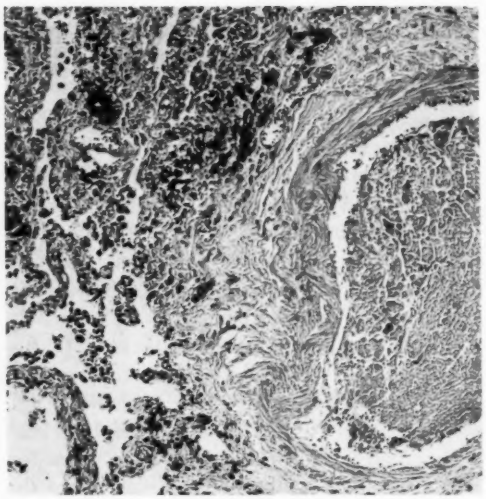


FIGURE 2. Tumor embolus in the lung.

intestine and in the colon; thus, the ulcer was presumably the source of bleeding. Another interesting finding was the presence of Meckel's diverticulum.

The microscopic sections provided the correct evaluation of this case, for the gross descriptions were more suggestive of primary lung tumor. A section through the bronchus which was most involved grossly showed an intact mucosa and tumor emboli in submucosal vascular structures (figure 1). Other lung sections showed similar metastatic foci (figure 2). Microscopic examination of the pancreas revealed the characteristic appearance of neoplastic duct structures in a wildly growing configuration (figure 3). Extensive vascular invasion was noted in the pancreas along with focal areas of fibrosis which altered the remaining normal pancreatic acini and ducts.

There were numerous other metastatic sites, some extremely unusual. These included the thyroid (figure 4), duodenal wall, rectum, adrenal glands and multiple lymph nodes. The duodenal metastasis was unrelated to the overlying benign ulcer. The gastrointestinal metastases and the history of multiple thromboses point to the body of the pancreas as the site of the primary tumor. This clinicopathologic association of coagulation abnormalities with pancreatic carcinoma is well recognized and currently is being extensively investigated.

DR. STANLEY LEITHOLD (attending physician in internal medicine): Both thrombosis and massive hemorrhage can occur in carcinoma of the pancreas. We have learned that at a fairly low concentration trypsin in the blood can act as a thromboplastic substance. This is illustrated by the fact that amniotic fluid acts as a thromboplastin in obstetric complications.

Intravascular thrombosis often occurs in the pancreas. If it occurs slowly, only thrombosis and thrombophlebitis result. On the other hand, as metastases occur there is more and more intravascular clotting, and what is known in the literature as the acute defibrinogenation syndrome develops. Thus, with massive intravascular clotting the level of the fibrinogen decreases and bleeding results.

This patient had an ulcer, and, as Dr. Kirshen mentioned, he probably had a hemorrhage with the administration of anticoagulants. However, the finding of a mass of ecchymosis at autopsy indicates that there probably was a coagulation defect, too. With this condition, trypsin can act as a fibrinolytic sub-

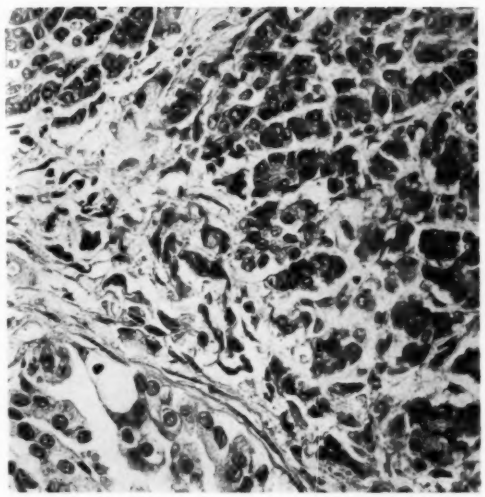


FIGURE 3. Primary adenocarcinoma of the pancreas.

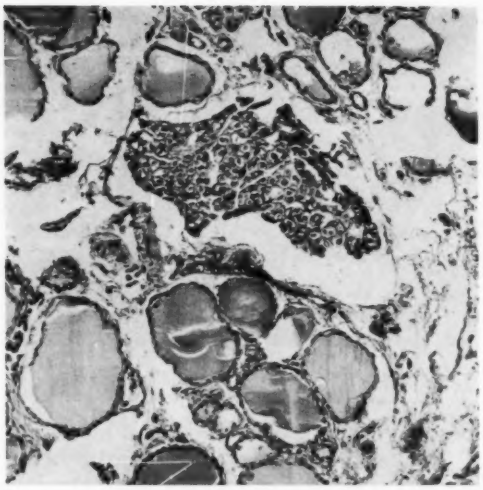


FIGURE 4. Tumor embolus in the thyroid.

stance; thus, along with the defibrinogenation, the fibrinogen content is lowered even more with a fibrinolytic situation. There are some trypsin inhibitors which can act as anticoagulants. We see this in carcinoma of the breast and particularly in carcinoma of the lungs, as Dr. Kirshen mentioned, because there also are thromboplastinlike substances in the lungs.

It is well to know about the situation of hypofibrinogenemia, because recognition of this condition may save the life of obstetric patients.

DR. ARMAND LITTMAN (chief of medical service): It is common for us to see a patient with thrombophlebitis. We may see only a single episode or perhaps thrombophlebitis in only one extremity. How much are we to make of this, Dr. Kirshen? Should we explore such patients? Do data indicate that we will find a curable carcinoma of the pancreas? How often does thrombophlebitis mean *only* thrombophlebitis?

DR. KIRSHEN: You cannot explore a patient on evidence of thrombophlebitis alone. Naturally, you must use your clinical judgment in such cases. If a patient who complains is "lucky," he may have gastrointestinal symptoms. As far as I know, the patient presented today did not have such symptoms. You can follow the course of acute thrombophlebitis. If acute thrombophlebitis heals and then occurs elsewhere three weeks later, something is wrong; there is carcinoma of the pancreas or lungs or some blood dyscrasia.

DR. LITTMAN: Can you assure us that this patient did not have a malignant Zollinger-Ellison tumor in view of the presence of the bleeding duodenal ulcer?

DR. KIRSHEN: I would like to say from a clinical viewpoint, not just to defend my diagnosis, that in such a case there would have been a different clinical course. Such patients are considered to have intractable ulcer, and they go on for years until someone decides to explore the pancreas. They have multiple bleeding and perforation; they are hospitalized several times during the course of their illness. The ulcers come close to perforation or actually perforate, and there is gastrointestinal bleeding. Clinically, such cases are unusual.

DR. VICTOR R. JABLOKOW (staff physician, laboratory service): Tumors associated with the Zollinger-Ellison syndrome are often benign and arise from the noninsulin-producing islet cells of the pancreas. They also may be malignant and produce massive metastases, as did the tumor in this patient.

Self-help Devices:

Grooming Aids

EDWARD W. LOWMAN AND HOWARD A. RUSK

Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

New York University-Bellevue Medical Center, New York

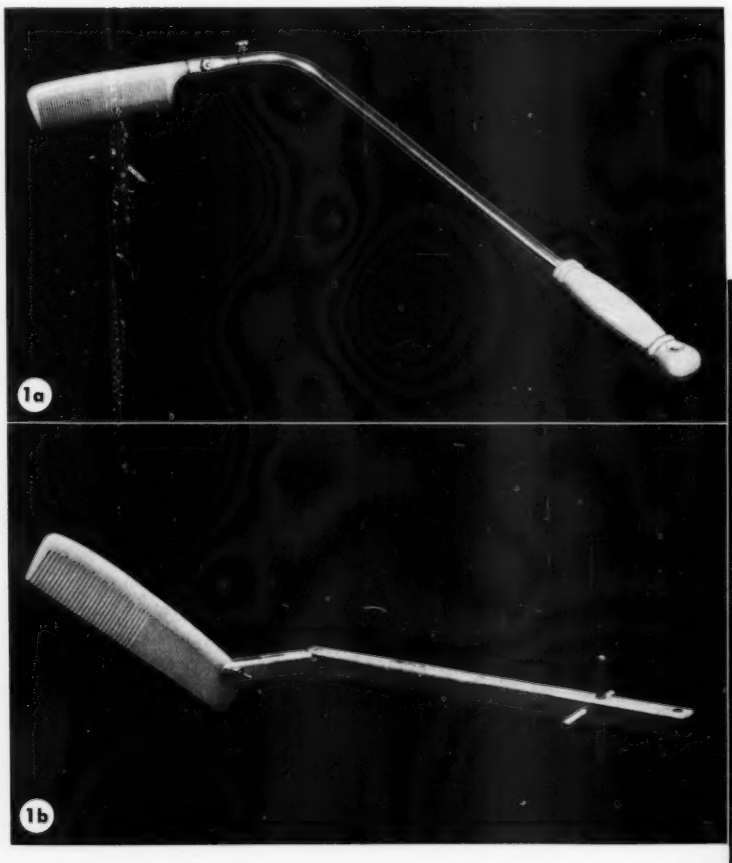


FIGURE 1. These combs are easily adjustable, offer extra reach, and have good handles for gripping. a. Available from Fascole, 229 Fourth Avenue, for $3.95. b. Available from Adjustics, 169 Thompson Street, for $2.50. c. Available from J. A. Preston, 175 Fifth Avenue, New York, for $6.00. Prices are approximate and do not include shipping charges.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

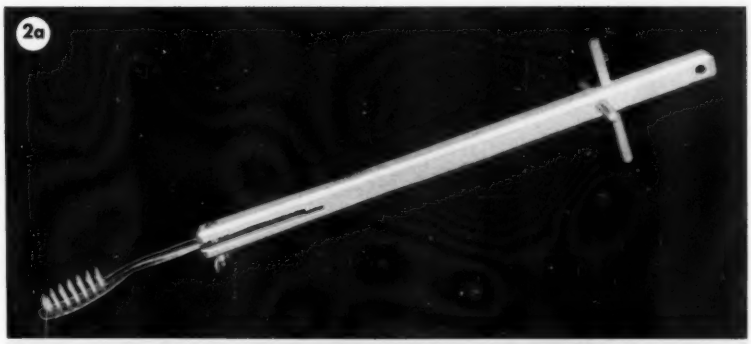


FIGURE 2. A standard toothbrush may be fixed to these extra long handles which are angled for convenient approach to the mouth and for use with either the right or left hand. a. Available from Adjustics for $2.35. b. Available from Fascole for $2.00. Prices are approximate and do not include shipping charges.

FIGURE 3. Around-the-neck mirrors are widely obtainable in many price ranges, depending on size and framing. This is an important device for the patient in a wheel chair who is unable to see into standard-height mirrors.

Lucite and glass model shown is inexpensive, lightweight, and easily adjustable to many different angles; it will also stand on a table surface. One side of the unit magnifies; the other is a plain mirror. Available from Fascole and other stores for about $1.95.

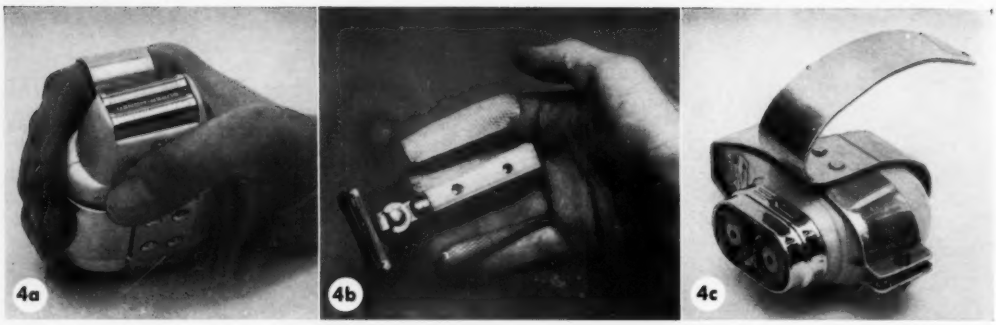


FIGURE 4a, b, c and d. For the man with disabled hands, shaving can be somewhat difficult. Electric shavers are energy savers, but they are sometimes awkward to hold. A variety of holders can be improvised from wood, sheet metal or plastic.

For the man who prefers the manual razor but lacks reach, the extra-long handle attachment is helpful. The company that designed and distributes this item does not plan to continue production. However, a similar device can be made by fitting a razor into a comfortable length of hollow metal or wood. The pegging at the handle is optional.

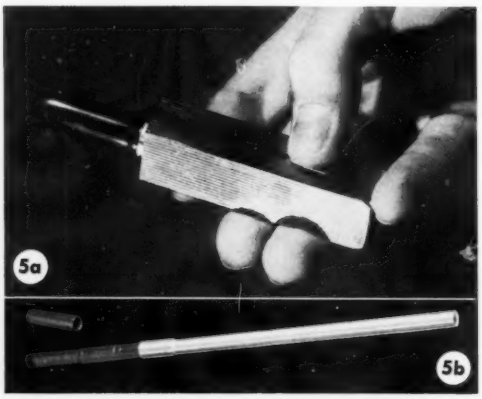


FIGURE 5. The application of face powder and lipstick is as essential to a woman as shaving is to a man.
a. The one-handed lipstick case does away with the necessity of removing, replacing and sometimes retrieving the cap of the standard lipstick case. One sliding motion with the thumb opens the case and moves the lipstick out ready for use. The flip-top case is available from stores carrying Hazel Bishop and Elizabeth Arden products.
b. If reach is the main problem, the lipstick may be mounted in the end of a piece of aluminum tubing for extra length.

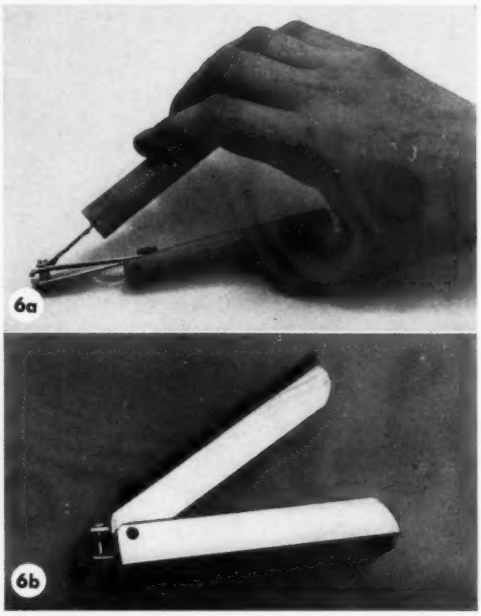


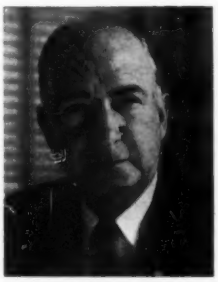
FIGURE 6. Cutting toenails is a problem that remains largely unsolved. Fingernails can be managed in several ways. Some patients, particularly those who must function singlehandedly, may be able to keep their nails trimmed by running them over a sheet of fine sandpaper.
a. A commercial nail clipper with home-devised enlarged handles may be used successfully by some patients.
b. The Handi-Clip is an easily operated clipper, which may be purchased from Scully Walton, 254 West 69th Street, New York, for about $1.50.

Readers are invited to submit suggestions and ideas for devices they have developed or know about and would like to share with others. Forward all comments and suggestions to: Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

The Small, Frantic Voice of the Patient

WILLIAM McPEAK*

The Ford Foundation, New York



WILLIAM McPEAK

THE theme of my paper is in its title: It is that the voice of the typical patient in his own ultimate welfare has too little influence in the practitioner's office and too much influence on the directions of medical research. In medical care he has too little power to act as his own spokesman; in research he is not sufficiently competent or objective to do so.

In medical care he is always the layman, dealing with the expert on the expert's ground and acting alone. He has no platform and is a member of no organized group that could lend weight to his questions and doubts. Furthermore, he is limited in choosing his doctor. With the present supply of physicians, he is a buyer in a seller's market, and his choice is confined usually to the local market. One of my premises is that this weakness in the patient's voice, together with the correspondingly dominant voice of the doctor, produces frequent dissatisfaction in the patient and can result on some occasions in substandard medical care.

In research, on the other hand, the patient and his family do have a voice. When reinforced by others, and further amplified during its transmission by special disease agencies, by philanthropists, by government legislators and government agencies, it swells into a vast chorus of dread and fear. It focuses on the disease that is dramatic, even though, like polio, it may not be widespread. And it focuses on the big killers like heart disease and cancer.

My second premise, in short, is that dread of dying from some dramatic disease produces in our national research effort an imbalance that must be redressed. The cost of this imbalance in dollars is substantial enough, but the cost in terms of social and psychologic values and in terms of diverting research talent from other important aspects of health is serious indeed.

The Patient and Medical Care

My discussion relates primarily to medical care of paying patients in the offices of private

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This is an adaptation of an address presented at the dedication of the new Stanford University Medical Center, Palo Alto, California.

practitioners, which is the bulk of all care. While hospital care is no less important, it is a vast subject in itself. My remarks will be confined largely to the shortcomings of current practice, for to dwell on the virtues would be far less helpful. America already has probably the best medical care in the world, but all of us are still interested in its continuing improvement.

The criticisms you will hear from me come from patients themselves. How valid their criticisms are, or how prevalent the practices criticized, you will know better than I. As a layman, I ask your indulgence to act as spokesman for the person to whom the entire medical enterprise is dedicated and devoted, namely, the patient.

If the patients' complaints about medical care were totaled, they would probably reflect less doubt of the doctors' competence, and less worry over excessive fees, than other concerns which go more directly to the heart of the doctor-patient relationship. Such concerns might be discussed under three headings: (1) the doctor's sense of personal convenience (and sometimes his profit), (2) the assertion of his expertise or his tone of omniscience, and (3) his general demeanor as a human being while dealing with other human beings during what are, *for them*, times of stress.

The problem of the doctor's sense of personal convenience can be located in all of the typical sites of medical care: the doctor's office, the home and the hospital. Many doctors' offices reflect a disregard for patients through their inefficient management, only one cost of which is the wastage of millions of hours of patient time. Too many doctors make appointments for as many as 20 patients at 2 o'clock on Wednesday. Such practices save the doctor little time or trouble, and therefore signify only selfishness or carelessness. Certainly they are unnecessary, as the practices of more considerate practitioners have demonstrated.

Another complaint concerns record keeping. By the time the average person arrives at middle age he has had several different types of medical treatment for different ailments by different doctors in different localities. Yet there is little system in present arrangements for intelligence to be communicated from one doctor to another. It is even difficult for a tuberculous patient, for example, to secure the old x-rays that a new doctor needs for a checkup.

One of the most common of all patient complaints is the difficulty of getting doctors to make house calls, especially at night and on week ends. Too frequently real disasters occur as a result. It is recognized that busy doctors must rest, and that they must not waste precious time and energy on querulous patients, but rules should not be so binding as to deny attention to the cases which seriously need it. The tendency to concentrate medical care in hospitals and doctors' offices, however numerous the advantages, has developed without full regard for the patient.

Unnecessary hospitalization can be laid at the door of the doctor only in part, however. The blame rests more upon our present systems of health insurance, which often provide no benefits for nonsurgical cases unless hospitalized. I cannot adequately develop this topic here but I would like to add that these systems badly need rationalization and that the doctor as a professional citizen, if not as a private practitioner, must accept some of the responsibility for leading the way.

Now for the patient's dependence upon the doctor's expertise. Here the doctor admittedly has to walk a narrow line on which the claims of scientific validity and professional responsibility impinge. Many traps are set out along this line and many doctor-patient relationships are caught in them.

One attitude of doctors that pains and frustrates the patient is that implied by his air of knowing all the answers. With many patients and in many situations this is a highly desirable form of reassurance, but in other cases it seems a transparent pretense. If so, the patient is likely to be worried and offended. The most troublesome situation is in the instance of differential diagnoses, when one doctor says one thing is wrong and another with equal assurance says the opposite. In such cases the patient is often at the doctors' mercy and he frequently follows one expensive and prolonged regimen after another. Sometimes such

cases can result from medical incompetence, but more often they probably result from a lack of frankness concerning the limits of medical science. If so, everyone would be better served if doctors would more often acknowledge that they don't know the answer. The doctor must recognize that to the extent he gives an impression of omniscience, to that extent the patient has the right to call on him for omnipotence as well!

Yet everyone knows that the present state of the science-art makes that impossible. With all respect to the triumphs of modern medicine, the questions remain.

Related to this is the practical difficulty a patient encounters in getting second or consulting opinions. It is asserted that in modern medicine no one is completely at the whim of the diagnosis or recommendation of one doctor alone, because the medical system freely honors the practice of consultation. The fact is, however, that the average patient with the average doctor is reluctant to request confirming opinions.

The third and last heading of patient concern is the doctor's basic attitude. Though intangible, it is nonetheless real, and it is at the bottom of most matters under discussion here.

Patients feel subordinated by the doctors not only medically but also personally. Too often their doctors strike them as either insensitive or indifferent. What undoubtedly is involved is a change in demeanor which has come with a change in professional role. As the doctor becomes more the specialized scientist, there necessarily follows a narrowing of the base for human contact. No one doubts that the shift in medicine has brought more gains than losses, but the gains do not permit us to ignore the losses, especially when the latter are so much in the patients' sphere. We must remember what medical care is all about and that the word "care" has a human, as well as a technical meaning.

During the past 50 years developments in public health have served people as patients or as potential patients in many important respects.

There have been similar welcome improvements in the attitude of organized medicine, especially over the past 20 years. However, in any patient-doctor relationship these organizations still are primarily spokesmen for the doctors and not for the patients.

After all of these complaints, it is time to get to the more important questions of what a medical center can do about them. I have three suggestions: One is to shorten the training time of doctors, one is to work to improve the immediate environment and systems of medical care, and the third is to give students realistic vocational preparation. No one of these is a new activity for our leading medical centers but they are all important enough to justify further discussion.

In speaking of shortening the training time we must consider not only the four years in medical school but all the time spanned by premedical preparation and final residency training.

My second suggestion, to try to improve the systems of medical care, is based on a simple hypothesis: The quality of a doctor's medical care is in large part a measure of the extent to which his work is subject to scrutiny by his professional peers. Most medical care takes place in the private office and is not subject to review. In the private practice of medicine, doctors for the most part are their own judges. This might not be so serious except that each therapeutic choice is, at one and the same time, a medical judgment and a business decision. Not always but frequently the choice of procedure involves the choice to collect a higher or lower fee, or none at all. This can be potent in solo practice, where the choice is presided over only by the lay patient and the doctor's own conscience. The mutual scrutiny of professional peers in some form of group practice would offer a higher quality of medicine, if my hypothesis is correct, and if, of course, the continuity of personal attention to the patient has not been sacrificed.

The third suggestion is to emphasize vocationalism. By this I mean to prepare the student with an accurate and unvarnished understanding of what medical care is in real life situations, especially in the offices of private practitioners.

In the vocational orientation courses sug-

gested here, which would be required and not elective, I would include the comparative study of health and medical practices in different countries.

Finally, I would concentrate heavily indeed on the nature of all variations in the medical care for patients in the general public, however practiced and however paid for.

The student must be made to address his questions not to our present doctors but to himself—the future doctor:

What sort of medicine will *he* provide when he first starts practice, perhaps in debt and short of patients?

How will *he* construe *his* responsibility when worried patients demand costly procedures or protracted care that is of doubtful value?

How will *he* behave when he simply doesn't know the answer? Will *he* prescribe all the tests available and simply fish for the answer? Or will he refer the patient? If so, to whom? The best man available, or some doctor better known to him?

What will *he* do when medical science has no answer? Or what will he do if medicine has only a very risky answer? Will *he* remember that nature too is a healer and follow the injunction inscribed at one of our great hospitals in Boston, which reads "*Primum non nocere*?" First of all do no harm.

Just how successfully will *he* maintain awareness of each patient as a human being? He may know that the word "patient" comes from a Latin form for one who "suffers" or "endures," but will he always remember that what was suffered or endured, in the original reference, was pain, not medical care?

Is he honest with himself concerning his deepest reasons for becoming a doctor? Does he know of the survey which showed that the students who most professed humanitarian reasons for studying medicine were the ones who likewise expected to make the most money from practice?

And what about his role in society? Will he pull his full weight as a citizen, or will he feel he is already doing enough good and succumb to the temptation to ignore charitable appeals and to evade some of his income tax?

In this important job of shaping proper attitudes, the task falls largely on the medical school. If the young doctor leaves medical school with the right attitudes, he will be armed for life.

The Patient and Medical Research

If the voice of the patient is too soft and weak in medical care, in research it is too loud and strong.

Patients and potential patients exert their strongest influence on medical research when affected by the fear of death. If all persons not immediately stimulated by the fear of death remain silent, or cannot make themselves heard on the subject of research, they are abdicating to those who act from the grip of fear. So long as this is true we can scarcely expect a balanced policy for research.

Even though I run the risk of seeming to argue for mystical or spiritual values, I am convinced that without realizing it we have become too preoccupied with the security and length of old age—with the quantity of life more than the quality of living. Further increments in the life span are not in and of themselves as important as what we accomplish and enjoy during life.

It would be fatuous to suggest that people now live too long, but it is not impertinent to question the wisdom of a limitless expansion of research attention to further increases in longevity at the expense of other research of equal importance.

There is no need for a moratorium on research of any kind but only for a rational balance. Perhaps this means first a balance between the rewards of research and the rewards for other efforts, so that those with lesser talent for research and greater talent for other pursuits will not be seduced into research activities of minimal and marginal promise. Secondly, there should be a better balance between research concentrated on the killer diseases and that devoted to other and equally important aspects of health, including such fields as psychiatry and psychosomatic medicine and the various phenomena affecting one's sense of physical well-being, such as energy, fatigue, stress and rest. The refocus might lead us to choose the greater emphasis

for the youth and vigor and health that is the quality of life, and let the quantity of life take second place.

All of you know that I am far from the first to discuss the general point of view expressed here, but some of you may not know that I was anticipated in its expression by almost 3000 years. Homer alluded to it in the fable of Aurora, the Goddess of the Dawn, and her husband Tithonus, who, though a highborn gentleman, was nevertheless a mortal. As Edith Hamilton tells it, "Tithonus had a strange fate. Aurora asked Zeus to make him immortal and he agreed, but she had not thought to ask also that he should remain young. So it came to pass that he grew old, but could not die. Helpless at last, unable to move hand or foot, he prayed for death, but there was no release for him. He must live on forever, with old age forever pressing upon him more and more. At last in pity the goddess laid him in a room and left him, shutting the door."

Summary

In medical care, I would have the medical center always think of itself as the friend of the patient and the molder of those who minister to his health.

In research, I would have the center assume the responsibility of spokesman, not only for the patient but for all society, in behalf of a saner policy than we laymen in our individual capacities can ever recommend, and indeed as a counter to our extreme influence.

I would not, as Aurora, request life everlasting, nor even ask, as she neglected to do, for perpetual youth. Instead I would content myself with the inalienable rights set forth in our Declaration of Independence, except that I would have a little less attention to the prolongation of life and, during the measure of life already given us, a little more attention to the health required for true liberty, and the vigor needed for a reasonably successful pursuit of happiness.

NEW STANFORD MEDICAL CENTER

Medical Progress in 1959

MORRIS FISHBEIN*

Chicago

AMONG medical announcements during 1959, the award of the Nobel prize to Drs. Severo Ochoa and Arthur Kornberg for the synthesizing of ribonucleic acid and desoxyribonucleic acid utilizing the action of enzymes was outstanding. This basic discovery advanced knowledge of genetics and perhaps also of various diseases.

Monoamine oxidase inhibitors were especially significant among new drugs. Important was the discovery of griseofulvin, apparently specific against various forms of ringworm. Synthesizing of penicillin and a number of new antibiotics were reported.

Biogenetics

The recent advances in biochemical genetics may provide a solution for the problem of cancer. They shed light on the nature of the genes and on the changes that take place in the genes leading to malformations of the body. Apparently the common denominator of all life may be nucleic acid as found in the nucleoproteins. The possible viral-nucleic acid origin of some cancers led to the concept of interconnection among viruses, cancer, genes and life itself. According to Dr. Wendell M. Stanley of the Virus Laboratory at the University of California, there is presumptive evidence that the genetic material of bacterial viruses is also desoxyribonucleic acid. He has said that the elucidation of the structure of nucleic acid in all its aspects is the most important scientific problem for investigation at this time.

Griseofulvin

Griseofulvin is obtained from a form of penicillin known as *Penicillium griseofulvum*, and is available under the trade names of FULVICIN® and GRIFULVIN®. In some severe instances involving ringworm of the feet, local treatment is combined with the antibiotic to secure prompt and completely effective results. Excellent reports have come that patients with ringworm of the scalp, the hands, the feet, the body and the groin all were benefited if not completely cured by the use of these drugs.

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Antibiotics

Dr. John C. Sheehan at Massachusetts Institute of Technology made pioneer studies and in 1950 managed to develop a substance called 5-phenyl-penicillin which, however, proved to be inactive. In 1957 he produced penicillin V which was synthetic but the process was too costly for practical use. In the course of these studies, an intermediate called 6-aminopenicillamic acid was found, and this has been the basis for development of several new synthetic penicillin compounds. In 1959 British scientists reported that they had succeeded in stopping the natural fermentation process immediately after formation of the nucleus and had extracted the 6-aminopenicillamic acid in amounts that could be usable and at low cost. Since this discovery some 500 new varieties of penicillin have been developed, all of which are under study as to their power to destroy germs and their freedom from undesirable effects on the body. At the annual antibiotic conference, held in November 1959, a new antibiotic from a sample of soil of Thailand was described. This substance, called Tylosin, is now undergoing tests as to its usefulness.

Five pharmaceutical companies market an antibiotic known as tetracycline under various trade names, and modifications of the original tetracycline have been offered with varying claims regarding their advantages one over the other.

In the attack on cancer some 50,000 antibiotic substances were being tested with funds from the National Institutes of Health, and more than 100 substances capable of inhibiting cancer growth were being further tested on animals and in some instances on human beings.

The widespread use of penicillin has led to the development of highly resistant bacteria, principally staphylococci which are uncontrollable by ordinary penicillins. Increasingly, infections with staphylococci were discovered, particularly in patients in hospitals, and new antibiotics of types different from penicillin are being used in an attempt to control them more successfully.

Endocrinology

One of the great advances was the preparation of ACTH in 1949. More recently three polypeptide hormones—oxytocin, vasopressin, and the melanocyte-stimulating hormone called MSH—have been synthesized. In many laboratories attempts are being made to synthesize ACTH which is the adrenocorticotropic hormone. The pituitary gland contains many other hormones and current research is endeavoring to separate gastrointestinal hormones, gonadotropins, the milk-stimulating and thyroid-stimulating hormones.

Resuscitation

The older methods of artificial respiration have now given way to the new technic of mouth-to-mouth breathing. Several plastic devices have been developed to aid in carrying out this technic. With the mouth-to-mouth devices, one end is inserted in the mouth of the unconscious person and the other in the mouth of the resuscitator. Resuscitation is carried out by alternate breathing in and out. If a device is not available, breathing mouth-to-mouth is necessary. Sometimes it is difficult to inflate the chest by this technic because the tongue falls back. The best step is to tilt the unconscious person's head backward and to keep the neck fully stretched, which gives a free passage of air from the mouth to the lungs. The person who is giving the resuscitation watches the chest of the unconscious person to make sure that it is being inflated. If the abdomen bulges, a slight steady pressure is made with one hand on the abdomen below the left ribs to aid the inflation and deflation of the lungs.

Rheumatoid Arthritis

Persons with rheumatoid arthritis have been found to have a form of gamma globulin in their blood which differs from that in people who do not have rheumatism. A test has been devised utilizing particles of latex or certain common clays which are coated with gamma globulin from the blood of normal people. When this material is mixed with serum from a person who has rheumatoid arthritis, the

particles agglutinate. The substance that causes this agglutination is the rheumatoid factor. Studies are being made to find out if this is in any way related to the cause of rheumatism. The substance has been injected into men and into animals but failed to produce rheumatoid arthritis. Its value in diagnosis is practically unquestioned.

Endogenous Depression and Monoamine Oxidase Inhibitors

Increase in cases of depression has led to the supplementation of ordinary psychotherapy with new drugs called monoamine oxidase inhibitors. These drugs block or counteract monoamine oxidase, an enzyme which is found in the body. Among the most widely known monoamines are serotonin and norepinephrine. The amines are important because they influence the blood pressure, people's emotions, and other functions of the body which cannot be controlled by will power alone. Until the advent of the monoamine oxidase inhibitors, electroshock treatment was the main method for treating severe depressions. The new drugs, which are called psychic energizers, have been used in a variety of conditions with numerous reports of great success. Already thousands of people have been treated with these new drugs which are marketed under a variety of trade names, such as NARDIL®, CATRON®, MARSILID® and NIAMID®.

Other varieties of drugs have been used in the attack on depression, including drugs that interfere with the alerting and arousal responses normally induced by pain. A combination of a tranquilizer called meprobamate with a substance called benactyzine has produced a drug called DEPROL® which has been used in neurotic depressions. Another drug, a precursor to acetylcholine, is called DEANER®. It seems to act on neurotic depression.

This field of investigation has yielded valuable drugs and because of their availability psychosurgery, involving removal of portions of the frontal lobe, is gradually disappearing.

Bone-marrow Infusions

Reports describing infusion of human bone marrow are steadily increasing. The bone marrow may be derived from the patient himself, from an identical twin, or from another person. In experimental treatments material from fresh cadavers or material removed at operation, such as the ribs or other bones, have been used. One use of the product is in the case of persons who are going to be treated with very powerful drugs used against cancer which may destroy bone marrow or interfere with its function of manufacturing blood cells. The material has also been used in patients with leukemia who have been heavily irradiated. The conditions which follow an excess of radiation, such as atomic accidents, are treated with infusions of bone marrow. Such infusions are used for people who have developed aplastic anemia in which the bone marrow of the patient fails to manufacture red blood cells. Reports say that human bone marrow will play an ever more important part in many aspects of medical care. Recent investigations have shown the possibility of taking bone marrow from the bones of healthy persons who have recently died and keeping it in marrow banks so that it will be available in serious cases of aplastic anemia.

Congenital Malformations

Following its success in developing a vaccine against infantile paralysis, the National Foundation has undertaken as a new program a study of congenital defects of infancy, principally hydrocephalus and spina bifida, but including also other abnormalities that may occur at birth. Lack of oxygen at the time of birth has been considered one cause of congenital deformities; another is infection with such viruses as those of German measles. Possibly, injuries at birth may also result in congenital malformation. An international congress will be held on the subject in London, July 18 to 22, 1960.

Some 60 different congenital diseases are now known which are due to a lack of an enzyme in the body. Among these are phenylketonuria and congenital galactosemia. In galactosemia a substance accumulates in the blood due to failure of the body to use it up because of a lack of the necessary enzymes. In time the accumulation of this compound causes

damage to the liver and the brain. These discoveries in biochemistry offer an explanation for a number of disturbances not heretofore understood.

Cancer

Outstanding in the advance against cancer has been the use of new substances made radioactive such as radioactive yttrium, which has been inserted into the pituitary gland, or radioactive gold used in the same way to destroy the pituitary and thus prevent the action of the growth hormone on cancer cells. The United States government has appropriated many millions of dollars now being used by some industrial companies which are studying the effects of many thousands of substances on cancer. A few substances which have been found capable of inhibiting cancer are being tested on animals and three such substances (5-fluorouracil, 5-fluorodeoxyuridine, and 6-azauracil) are now undergoing active study on patients in hospitals devoted to the care of those with cancer.

Cytologic studies are made of cells taken from various organs and tissues of the body. Examination of these cells permits determination of the presence or absence of cancer. An electronic device has been developed which can examine specimens of tissues taken particularly from the uterus. A report from the National Cancer Institute said that the cytoanalyzer had been used to examine 1,075 negative slides and 20 positive or suspected-positive slides. The machine has been proved to be accurate and some hundreds of thousands of women have already had examinations in which the cytoanalyzer was used.

In St. Thomas Hospital, London, a new development in the treatment of cancer involves a device in which living cells are destroyed by ionizing radiation which acts in the presence of oxygen which is concentrated around the cells at the time of irradiation. The patient lies in an aluminum cylinder pressure chamber; when he is surrounded by oxygen, he is exposed to a cobalt unit which rotates at various speeds around the patient. The treatment has been used on 80 patients and is more efficient than previous technics.

When cancer cells grow, they use a protein called glutamine which helps to make the nucleic acid of the cell. At the City of Hope Medical Research Institute a biochemist named Eugene Roberts is seeking a glutamine antagonist with the hope that interference with the use of glutamine by cancer cells would lead to their control or destruction. Several glutamine antagonists now being investigated in various institutes show promise of being useful in the treatment of cancer.

A new procedure in the treatment of cancer involves isolation of cancers by surgery and then perfusing the cancer with blood from an outside source to which has been added a far greater amount of 5-fluorouracil than could be tolerated by the person due to the effects of the drug on the bone marrow and the lining of the digestive tract. At Duke University scientists found that heating the body to 105° F. before adding the drug gave it increased potency against cancer cells.

Air Pollution

During 1959 a conference was held in Washington, D.C., under the auspices of the Department of Health, Education, and Welfare. Testimony from many experts showed that air pollution is becoming an increasing hazard to health. Some scientists felt that the increase in air pollution is in some way related to the apparent rise in cancer of the lung during the past 25 years.

Cystic Fibrosis

In this condition the primary defect is in the glands of the lungs, the pancreas, the liver, the skin and also the salivary glands. The glands secrete a thick mucus which is not easily removed, causing an infection of the lining of the bronchial tubes and obstruction to breathing. Such patients also produce an abnormal form of sweat. In a test devised by workers at Ohio State University, it is possible to diagnose cystic fibrosis by examining the sweat itself. The sweat is collected on sponges attached to the body of the person who is sealed in a bag and submitted to high temperatures for a little over an hour. The fluid is then examined for its content of sodi-

um and chloride which gives an indication of the absence or presence of cystic fibrosis.

Detached Retina

When the retina becomes detached from the tissues on which it rests, vision disappears. A new treatment developed in Germany involves exposure of the retina to rays of the sun through a device which directs a beam of extremely hot light waves through the dilated pupil to a spot on the underlying tissues opposite the torn place in the retina. Just one flash of light focused on such a spot is sufficient to set up an inflammatory reaction which seals the retina to the choroid and closes the torn area. This is called photocoagulation.

Memory

In the Montreal Neurological Institute of McGill University, Dr. Wilder Penfield detected an area on the surface of the human brain where electrical stimulation brought back a sequence of past experiences. In an operation with the brain exposed, an electrode applied to the right temporal lobe regularly produced a dream which re-enacted a childhood experience. Dr. Penfield explains that a steady stream of electric pulses applied through an electrode to a point in this area of the brain, called the interpretive cortex, causes a stream of excitation to flow from the cortex to the place where the past experience is recorded. The stimulation can enter the pathway of recorded consciousness at any random point from childhood on to adult life. When the experience enters consciousness, memory moves forward without interference from other experiences.

Heart, Cholesterol and Circulation

Cholesterol continues to attract attention as a major factor in the production of hardening of the arteries and of coronary thrombosis. The cause of atherosclerosis is still not known. Much evidence indicates that it is related to the metabolism of fats. Hence physicians are encouraging reduction of fats in the diet and lowering of weight in an attempt to reach normal cholesterol values. Various drugs and diets are known which can reduce a high level of cholesterol in the blood.

A report to the American Heart Association indicted ADRENALIN® and NORADRENALIN® as hormones which tend to raise blood pressure particularly in persons who overwork or who work under stress.

Late in 1959, a report appeared indicating a "prudent diet" for lowering cholesterol with adequate amounts of high-grade protein at each meal made up of such foods as cottage-type cheese, fat-free milk, chicken, turkey, veal, leaner cuts of beef, mutton, lamb and pork (with all visible fat removed), fish, seafood and egg whites. When fat is required to prepare food, linoleic acid (which is believed to lower blood cholesterol), an 80 per cent unaltered corn oil margarine, corn oil, or an emulsion of corn oil may be used. A person who wishes to lower blood cholesterol should not eat—except under unusual circumstances—butter, ordinary (partially hydrogenated) margarine and shortenings, lard or cream, or foods containing them in large amounts, such as most cakes and pastries. A special 80 per cent unaltered corn oil margarine, called EMDEE® margarine, has a high linoleic acid content.

Surgery of the Heart

In heart surgery two great advances involved the use of the heart-lung machine in operating on two patients in succession and thus lowering greatly the amount of blood required for transfusion, and the operation developed by Dr. Michael E. DeBakey of Baylor University in dissecting aneurysms of the aorta. This Houston clinic now has a record of more than 2500 operations on damaged arteries in the past 10 years. Another report has been made of 107 operations to correct damage done to the aortic valve, which governs the blood flow from the heart into the aorta.

Another report describes surgery on the open heart to correct disease of the pulmonary valve which controls the flow of blood from the heart to the lungs.

In the operation of the heart-lung machine, Dr. Robert E. Gross, who received the Lasker Award for his work, notes that the machine

TABLE 1

AVERAGE WEIGHTS OF WOMEN

Graduated Weights (in Indoor Clothing) in Pounds

HEIGHT	AGE GROUPS							
	15-16	17-19	20-24	25-29	30-39	40-49	50-59	60-69
4′ 10″	97	99	102	107	115	122	125	127
11″	100	102	105	110	117	124	127	129
5′ 0″	103	105	108	113	120	127	130	131
1″	107	109	112	116	123	130	133	134
2″	111	113	115	119	126	133	136	137
3″	114	116	118	122	129	136	140	141
4″	117	120	121	125	132	140	144	145
5″	121	124	125	129	135	143	148	149
6″	125	127	129	133	139	147	152	153
7″	128	130	132	136	142	151	156	157
8″	132	134	136	140	146	155	160	161
9″	136	138	140	144	150	159	164	165
10″	*	142	144	148	154	164	169	*
11″	*	147	149	153	159	169	174	*
6′ 0″	*	152	154	158	164	174	180	*

*Average weights omitted in classes having too few cases.

TABLE 2

AVERAGE WEIGHTS OF MEN

Graduated Weights (in Indoor Clothing) in Pounds

HEIGHT	AGE GROUPS							
	15-16	17-19	20-24	25-29	30-39	40-49	50-59	60-69
5′ 0″	98	113	122	128	131	134	136	133
1″	102	116	125	131	134	137	139	136
2″	107	119	128	134	137	140	142	139
3″	112	123	132	138	141	144	145	142
4″	117	127	136	141	145	148	149	146
5″	122	131	139	144	149	152	153	150
6″	127	135	142	148	153	156	157	154
7″	132	139	145	151	157	161	162	159
8″	137	143	149	155	161	165	166	163
9″	142	147	153	159	165	169	170	168
10″	146	151	157	163	170	174	175	173
11″	150	155	161	167	174	178	180	178
6′ 0″	154	160	166	172	179	183	185	183
1″	159	164	170	177	183	187	189	188
2″	164	168	174	182	188	192	194	193
3″	169	172	178	186	193	197	199	198
4″	*	176	181	190	199	203	205	204

*Average weight omitted in class having too few cases.

must be primed with 1 to 4 pt. of freshly drawn blood and up to 30 pt. may be needed for transfusions and as a reserve in operations on the heart. The blood must be carefully matched to the patient's blood group on the day before or the day of the operation and treated to reduce clotting. Stored blood is not usable.

New Drugs

In any one year in the United States more than 300 new preparations and modifications of older drugs may be introduced for general use by the medical profession. Among the outstanding developments of 1959 may be mentioned the psychic energizers; new methods

for preparing a form of cortisone which is much more powerful than those previously known; antibiotic drugs, including particularly several from Japan such as kanamycin and Colimycin, and various antihistamine mixtures designed to cover more indications than individual drugs previously known. New dosage forms provide for more palatable drugs and also for delayed-action capsules which permit the release of one drug immediately and the other layers at various intervals.

Height and Weight Standards

In October 1959 the Society of Actuaries, representing 26 leading insurance companies of the United States, published a report of their experience relating to varying body build, blood pressure, height and weight, and the relationship of obesity and high blood pressure to life expectancy. War deaths were excluded. As a result new tables of weights and heights for both women and men were developed which differ from those previously in use (tables 1 and 2).

The average weight of women is less now than it was 40 years ago, and the average weight of men is more. The proportion of men who are underweight has lessened and the proportion of underweight women has increased. Men who weigh 20 lb. above the average have about 10 per cent higher mortality; when men are 25 lb. above the average, their excess mortality is 25 per cent. The figures prove that persons who are overweight and who reduce can increase their life expectancy as long as they keep their weight down. Teen-agers who are slightly overweight have better expectancy than those who are underweight.

In general the average weight of men increases by 4 to 5 lb. for every inch of height. For very short men the increase is 3 lb. for every inch; for tall men, 6 lb. per inch. Similarly the average weight of women increases 3 to 4 lb. for every inch. The increase is 2 lb. for short women and for tall women as much as 5 or 6 lb. The proportion of overweights is greater in women than it is in men after the age of 30.

Tall men have lower mortality rates than short ones at most ages. In general people who weigh more than 254 lb. carry an extra hazard for early mortality. A high death rate from diseases of the heart and circulatory system is the principal reason for excess mortality in overweight men with high blood pressure. Among hazards which were investigated were rapid pulse, heart murmurs, varicose veins, hardening of the arteries, albuminuria, digestive disorders, and nervousness. Actually a record of dyspepsia, indigestion, gastritis, cardiospasm and pylorospasm offers less hazard than does nervousness, particularly when such conditions as psychasthenia and nervous indigestion occur at a young age.

MEETINGS *and Postgraduate Courses*

INTERNATIONAL CONFERENCE OF SURGEONS, TEL AVIV AND JERUSALEM, ISRAEL: To be held May 21-23. Program will include symposia on various surgical fields. For further information, write to: International Secretariat, International College of Surgeons, 1516 Lake Shore Drive, Chicago, or Israel Government Tourist Office, 5 South Wabash Avenue, Chicago.

THE NATIONAL FOUNDATION, NEW YORK: Fellowships for clinical study in arthritis and related diseases are available for physicians who intend to apply their knowledge of these diseases to clinical service, teaching or research. Applicants must be United States' citizens who are licensed or eligible for licensure to practice in the United States and who have had at least two years of specialty training acceptable to the appropriate American board (or equivalent training).

Fellowships are awarded for one year and may be renewed. Financial support is $4500 yearly plus dependent allowances and annual increases. Complete tuition and fees are paid for a full academic program.

Applications are due February 1, August 1, and November 1 for consideration three months later.

For further information, write to: Division of Scholarships and Fellowships, Department of Professional Education, The National Foundation, 800 Second Avenue, New York 17.

WESTERN RESERVE UNIVERSITY, CLEVELAND: The Law-Medicine Center will present an institute on "The back: A law-medicine problem reappraised," at the Hatch Auditorium, February 12-13. For further information, write to: Oliver Schroeder, Jr., The Law-Medicine Center, Western Reserve University, Cleveland 6.

	ALLERGIC EMERGENCIES
	ACUTE ASTHMA
	EMERGENCY SURGERY
	OVERWHELMING INFECTIONS
	TRANSFUSION REACTIONS
✓	SHOCK
	ACUTE TRAUMATIC INJURIES

to immediate corticosteroid benefits

INJECTION

Decadron® PHOSPHATE

DEXAMETHASONE 21-PHOSPHATE

- *ready for use immediately*
- *effective immediately*

mg. for mg. the most active steroid in true solution

- needs no reconstitution—ready for immediate use
- needs no refrigeration—excellent stability
- potency up to 40 times that of hydrocortisone
- dramatic response in minutes I.M. or I.V.—injection can be as rapid as desired
- in true solution—flows readily even through a small-bore needle

Injection DECADRON Phosphate can also be used in acute dermatoses, Addison's disease, adrenal surgery, panhypopituitarism, temporary adrenal suppression, rheumatoid arthritis, soft-tissue injection. Note: Do not inject into intervertebral joints. Caution: Steroids should not be given in the presence of tuberculosis, chronic nephritis, acute psychosis, peptic ulcer, or ocular herpes simplex.

DOSAGE AND ADMINISTRATION: Injection DECADRON Phosphate is ready for immediate use intravenously, intramuscularly, or intra-articularly. Dosage varies from 4 mg. or less to 20 mg. or more, depending on the nature and severity of the condition.

SUPPLIED: Injection DECADRON Phosphate is available in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21-phosphate as the disodium salt.

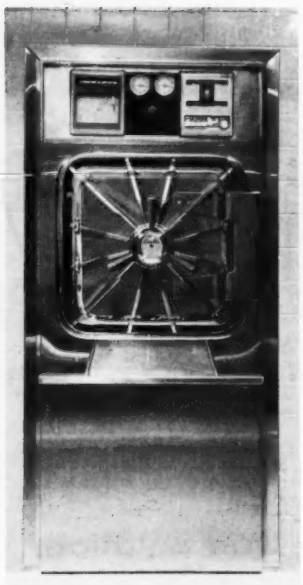
Literature on Injection DECADRON is available at your request.

DECADRON is a trademark of Merck & Co., INC.

MERCK SHARP & DOHME
Division of Merck & Co., INC., Philadelphia 1, Pa.

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.



• ORTHOMATIC STERILIZER

DESCRIPTION: Featuring substantially reduced cycle time, this unit is operated by four completely automatic keyboard controls. Cycle temperature can be varied between 220 and 270° F. The refrigerant cooling system cools a full load in an average of 20 minutes, and the drying timer is calibrated to the minute. The sterilizer is available in cabinet or recessed mountings, with cylindrical, straight-line or rectangular bodies.
PRODUCER: Wilmot Castle Co., Rochester, N.Y.

• ANTI-M LECTIN

PURPOSE: Blood-typing reagent.
COMPOSITION: Purified extract from the seed of *Iberis amara*.
HOW SUPPLIED: 2 cc. dropper vials.
PRODUCER: Hyland Laboratories, Los Angeles, a subsidiary of Baxter Laboratories, Inc., Morton Grove, Ill.

• FORTESPAN®

PURPOSE: Nutritional therapy.
COMPOSITION: Each sustained-release capsule (SPANSULE®) contains nine vitamins.
DOSAGE AND ADMINISTRATION: 1 capsule daily, on arising or at breakfast.
HOW SUPPLIED: Bottles of 30 and 100.
PRODUCER: Smith, Kline & French Laboratories, Philadelphia.

• PROLIXIN

PURPOSE: To treat mental disorders.
COMPOSITION: Fluphenazine dihydrochloride.
DOSAGE AND ADMINISTRATION: Single daily doses for most patients.
HOW SUPPLIED: 1, 2.5 and 5 mg. tablets in bottles of 50 and 500.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

(Continued on page A-124)

new Noludar 300

300 mg CAPSULES

A good night's sleep can be described in many ways, but "natural" comes closest to the kind of sound, refreshing sleep your patients will enjoy when you prescribe new NOLUDAR 300. Prompt action ... unsurpassed safety ... 6 to 8 hours of undisturbed rest ... and a cheerful awakening without "hangover"—such is the quality of sleep with NOLUDAR. *Well tolerated, non-barbiturate, non-addictive, virtually free of even minor side reactions.* DOSAGE: Adults—One 300-mg capsule before retiring. Also available in 200-mg tablets for gentle hypnotic effect and 50-mg for daytime sedation.

NOLUDAR®—brand of methyprylon

ROCHE LABORATORIES · Division of Hoffmann-La Roche Inc · Nutley 10, New Jersey

• OTRIVIN®

PURPOSE: Nasal decongestant.
COMPOSITION: Xylometazoline.
HOW SUPPLIED: 0.1 per cent solution in 30 ml. dropper bottles and 15 ml. plastic squeeze tubes; 0.05 per cent solution for pediatric use in 15 ml. plastic squeeze tubes.
PRODUCER: Ciba Pharmaceutical Products, Inc., Summit, N. J.

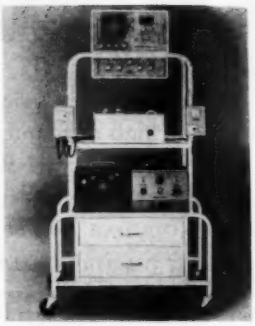
• EXPENDABLE PLASTIC OXYGEN MASK

DESCRIPTION: Used with standard oxygen connecting tubes or large-bore tubing, the mask is made of a nontoxic green vinyl which conforms to the face. It remains soft and pliable when in use, can be trimmed with shears to conform to unusual facial features, and has a breathing bag for use with high concentrations of oxygen.
PRODUCER: National Cylinder Gas Division of Chemetron Corporation, Chicago.

• QUELICIN® CHLORIDE (New Package Form)

PURPOSE: Muscle relaxant.
COMPOSITION: Each milliliter contains 25 mg. succinylcholine chloride.
CAUTION: Large doses cause respiratory depression, and facilities for artificial respiration should be immediately available. Only persons skilled in administering oxygen and controlled respiration should use this drug. It is contraindicated in patients with severe liver disease, anemia and malnutrition and in insecticide poisoning. Anticholinesterases are contraindicated as antidotes.
DOSAGE AND ADMINISTRATION: For short procedures, single doses of 10 to 30 mg. administered intravenously. For long procedures, 0.1 or 0.2 per cent solution of Quelicin in isotonic saline solution or in 5 per cent dextrose in water administered by the intravenous drip technic; the rate of flow should be regulated from 0.5 to 3.25 ml. (0.5 to 6.5 mg.) per minute, depending on the patient's response.
HOW SUPPLIED: 20 and 40 ml. ABBO-VIAL® containers; also available in 10 ml. multiple-dose vials containing 20 mg. per milliliter and in 10 ml. ampules containing 50 or 100 mg. per milliliter (for dilution only).
PRODUCER: Abbott Laboratories, North Chicago.

• CARDIAC MONITORING AND RESUSCITATION CENTER (Model 390)



DESCRIPTION: The Birtcher Center provides all of the necessary electronic instruments for cardiac monitoring and resuscitation procedures. The unit is mounted on a 5 ft. mobile pyramid cabinet and is comprised of a cardioscope, EEG pre-amplifier, an electronic switch for providing a dual tracing, defibrillator, and heartpacer. All necessary cables and standard accessories for each instrument are included. Two large drawers in the cabinet provide ample storage space.
PRODUCER: The Birtcher Corporation, Los Angeles.

• INJECTABLE B_{12} PLEX® WITH C

PURPOSE: To treat vitamin B complex and ascorbic acid deficiencies.
COMPOSITION: Vitamin B_{12}, ascorbic acid and the water-soluble B vitamins.
DOSAGE AND ADMINISTRATION: When given undiluted, no more than 2 cc. should be administered by slow intravenous or intramuscular injection. The solution may be added to parenterally administered nutritional fluids.
PRODUCER: Philadelphia Ampoule Laboratories, Philadelphia.

• GUAIAHIST TT

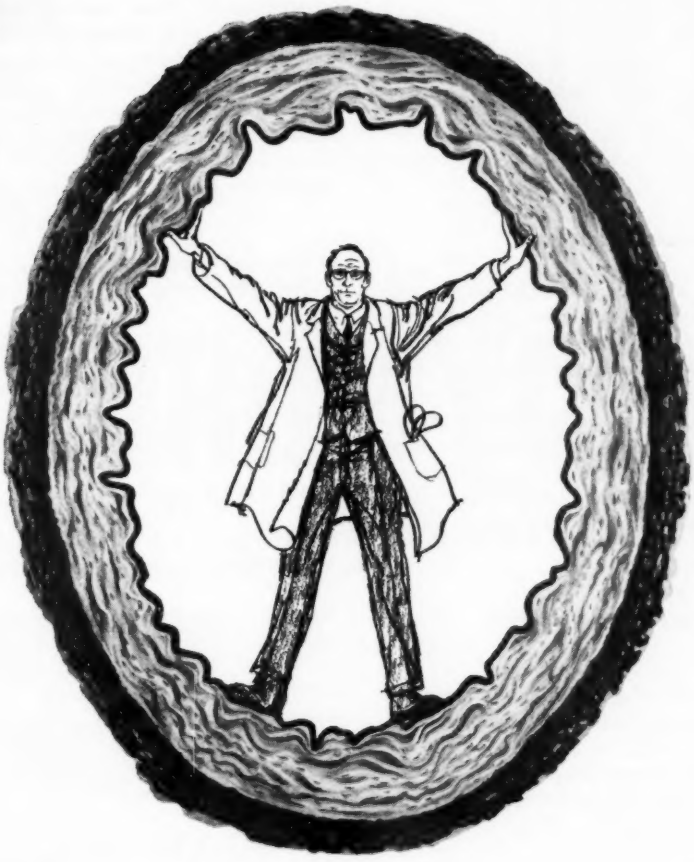
PURPOSE: To provide sustained decongestive and antitussive therapy.
COMPOSITION: Each tablet contains:

Phenylephrine hydrochloride	20 mg.
Chlorpheniramine maleate	4 mg.
Glyceryl guaiacolate	300 mg.

DOSAGE AND ADMINISTRATION: 1 or 2 tablets twice a day.
HOW SUPPLIED: Bottles of 50 and 500.
PRODUCER: Columbus Pharmacal Company, Columbus, Ohio.

(Continued on page A-126)

in coronary insufficiency



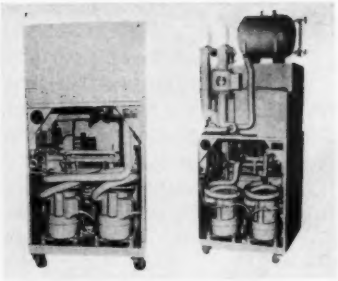
Metamine® Sustained* helps you dilate the coronaries

METAMINE SUSTAINED (triethanolamine trinitrate biphosphate, 10 mg., in a unique sustained-release tablet) is a potent and exceptionally well tolerated *coronary* vasodilator. Pharmacological studies at McGill University demonstrated that METAMINE "exerts a more prolonged and as good, if not slightly better coronary vasodilator action than nitroglycerin . . . "[1] Work at the Pasteur Institute established that METAMINE exerts considerably less depressor effect than does nitroglycerin.[2] Virtually free from nitrate side effects (nausea, headache, hypotension), METAMINE SUSTAINED protects many patients refractory to other cardiac nitrates,[3] and, given b.i.d., is ideal medication for the patient with coronary insufficiency. Bottles of 50 and 500 tablets. Also: METAMINE, METAMINE WITH BUTABARBITAL, METAMINE WITH BUTABARBITAL SUSTAINED, METAMINE SUSTAINED WITH RESERPINE.

1. Melville, K. I., and Lu, F. C.: Canadian M.A.J., *65*:11, 1951. 2. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap., *83*:367, 1946. 3. Fuller, H. L., and Kassel, L. E.: Antibiotic Med. & Clin. Therapy, *3*:322, 1956.

Thos. Leeming & Co. Inc. New York 17, N. Y.

*Patent applied for



• KOLD-PAK REFRIGERATION EQUIPMENT

DESCRIPTION: A portable, packaged remote supply of refrigeration, this one-piece assembly provides temperatures as low as –120° F. to any enclosure. Twelve standard models can be obtained in either the direct expansion type (left) or the brine chiller type (right). Caster-mounted for mobility, this equipment refrigerates an independently built work space or augments the capacity of other refrigeration equipment.
PRODUCER: Tenney Engineering, Inc., Union, N. J.

• SURGAMYCIN TOPICAL SPRAY OINTMENT

PURPOSE: Antibiotic.
COMPOSITION: Each 30 gm. contains 15 mg. tetracycline hydrochloride and 15 mg. neomycin sulfate per gram of ointment.
HOW SUPPLIED: In aerosol cans.
PRODUCER: American Cyanamid Company, Surgical Products Division, New York.

• K-PLEX SYRUP

PURPOSE: Potassium replacement therapy.
COMPOSITION: Each teaspoonful (5 cc.) contains:

Potassium	295 mg.
Thiamine mononitrate	1 mg.
Riboflavin	0.5 mg.
Pyridoxine hydrochloride	0.5 mg.
Niacinamide	3.5 mg.

CAUTION: Therapy should not be started in the presence of inadequate urinary output or impaired kidney function.
DOSAGE AND ADMINISTRATION: 1 or 2 teaspoonfuls three times a day or as indicated.
HOW SUPPLIED: 1 pt. bottles.
PRODUCER: Walker Laboratories, Inc., Mount Vernon, N.Y.

• SYNCILLIN®

PURPOSE: Antibiotic.
COMPOSITION: When reconstituted with water, Syncillin for oral solution provides 125 mg. potassium alpha-phenoxyethyl penicillin per 5 cc.; 250 and 125 mg. Syncillin tablets provide 400,000 and 200,000 units penicillin, respectively.
HOW SUPPLIED: Solution in 60 cc. bottles; tablets in bottles of 25.
PRODUCER: Bristol Laboratories, Inc., Syracuse.

• SUMYCIN® PRESSULES
(New Product Form)

PURPOSE: To treat common pediatric infections.
COMPOSITION: Each pressule contains 100 mg. tetracycline in an aqueous suspension potentiated with potassium metaphosphate.
HOW SUPPLIED: Packages of 12.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• CYCLOBAR®

PURPOSE: Cycloplegic and antibiotic agent.
COMPOSITION: CYCLOGYL® and neomycin in a gel form.
HOW SUPPLIED: 3.54 gm. tubes.
PRODUCER: Schieffelin & Co., New York.

• NOLAMINE EXPECTORANT

PURPOSE: To relieve coughing.
COMPOSITION: Each teaspoonful (5 ml.) contains:

Glyceryl guaiacolate	50 mg.
Dihydrocodeinone bitartrate	1.70 mg.
Chlorprophenpyridamine maleate	0.67 mg.
Phenindamine tartrate	4 mg.
Phenylpropanolamine hydrochloride	8.35 mg.

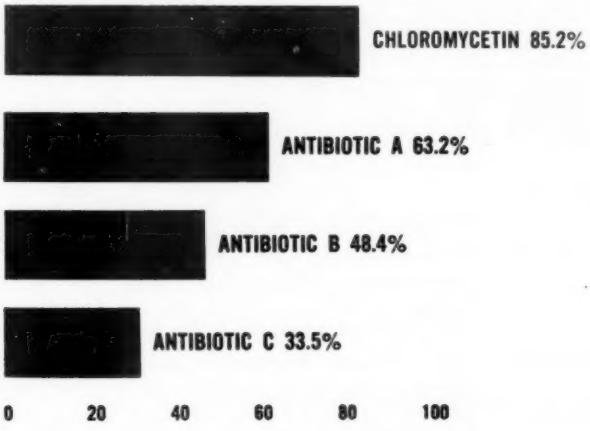
CAUTION: Use with caution in hyperthyroid and hypertensive patients and those sensitive to antihistamines.
DOSAGE AND ADMINISTRATION: Adults, 1 or 2 teaspoonfuls every four hours; children aged six and older, 1 teaspoonful every four hours, and aged one to six, ¼ to 1 teaspoonful every four hours according to age and weight.
HOW SUPPLIED: 16 oz. bottles.
PRODUCER: G. W. Carnrick Company, Newark, N. J.

(Continued on page A-128)

WHEN EVEN STUBBORN HOSPITAL STAPHYLOCOCCI RESPOND... THE ANTIBIOTIC IS APT TO BE

CHLOROMYCETIN®

IN VITRO SENSITIVITY OF 337 STRAINS OF PATHOGENIC STAPHYLOCOCCI (ISOLATED FROM HOSPITAL PATIENTS) TO CHLOROMYCETIN AND TO THREE OTHER ANTIBIOTICS*



*Adapted from Goslings, W. R. O., & Büchli, K.: *Arch. Int. Med.* 102:691, 1958.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its use, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

89259

• HIGH-TEMPERATURE OVEN

DESCRIPTION: Designed for laboratory use, this unit provides constant and uniform heat for long periods. Its interior is constructed of stainless steel supplied by the Allegheny Ludlum Steel Corporation. Electric resistance heaters are located in all six walls. Temperature range is 125 to 1000° F.; heat-up time from room temperature to 725° F. is one hour. Controls include an electronic, thermistor-type temperature controller; a controller for a predetermined average wattage; a master switch and pilot light, and an adjustable safety thermostat. The unit weighs about 200 lb. and has an interior work area measuring 20 by 19 by 18 in.
PRODUCER: American Instrument Company, Inc., Silver Spring, Md.

• HYCOMINE® SYRUP
(New Formula)

PURPOSE: Antitussive, expectorant and nasal decongestant.
COMPOSITION: Each teaspoonful (5 cc.) contains:

HYCODAN® (5 mg. dihydrocodeinone bitartrate and 1.5 mg. homatropine methylbromide)	6.5 mg.
Pyrilamine maleate	12.5 mg.
Phenylephrine hydrochloride	10 mg.
Ammonium chloride	60 mg.
Sodium citrate	85 mg.

CAUTION: Drug is a class B narcotic and may be habit-forming.
DOSAGE AND ADMINISTRATION: Usual adult dosage is 1 teaspoonful after each meal and at bedtime with food. Dosage for children varies according to age.
HOW SUPPLIED: 1 pt. and 1 gal. bottles.
PRODUCER: Endo Laboratories, Inc., Richmond Hill, N.Y.

• ATARAX® PARENTERAL SOLUTION
(New Dosage Form)

PURPOSE: Tranquilizer.
COMPOSITION: Each cubic centimeter contains 50 mg. hydroxyzine hydrochloride.
DOSAGE AND ADMINISTRATION: Intravenously or by deep intramuscular injection.
HOW SUPPLIED: 2 cc. ampules.
PRODUCER: J. B. Roerig and Company, division of Chas. Pfizer & Co., Inc., New York.

• "460" PRESSURIZED BLOOD TRANSFUSION SET

DESCRIPTION: With this unit, blood may be administered to the patient either by gravity feed or under pressure without danger of air embolism. The set consists of a polyvinyl envelope which is divided into sealed chambers for blood and for air. Capacity of the blood chamber exceeds 700 cc. Blood is prefiltered through 8 sq. in. of filtering surface as it enters the chamber. It then may be transfused into the patient by gravity. A few squeezes on a detachable pressure bulb quickly pressurize the transfusion. The inflated air chamber exerts a constant pressure on the blood, resulting in a smooth, even flow to the patient.
PRODUCER: American Sterilizer Company, Erie, Pa.

(Continued on page A-130)

predictable weight loss

FOR THE VICTIM OF OVEREATING AND "UNDERDOING"...

℞

BIPHETAMINE®

A 'STRASIONIC' RELEASE ANORETIC RESIN

Employing 'Strasionic' release, Biphetamine's appetite appeasing, mildly invigorating action is uniformly prolonged for 10 to 14 hours with a single capsule dose. Caloric intake is reduced, energy output is increased. Weight loss is predictable—a comfortable 1-3 lbs. a week in 9 out of 10 cases.

"STRASIONIC RELEASE" MAKES THE BIG DIFFERENCE

BIPHETAMINE® '20' Resin
Each black capsule contains:
d-amphetamine ..... 10 mg.
dl-amphetamine ..... 10 mg.
as resin complexes

BIPHETAMINE® '12½' Resin
Each black and white capsule contains:
d-amphetamine .....6.25 mg.
dl-amphetamine .....6.25 mg.
as resin complexes

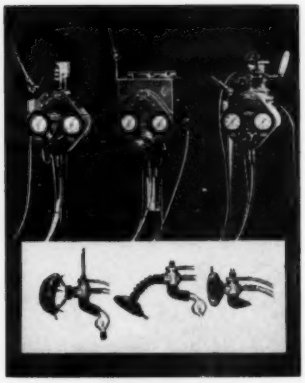
BIPHETAMINE® '7½' Resin
Each white capsule contains:
d-amphetamine .....3.75 mg.
dl-amphetamine .....3.75 mg.
as resin complexes

Single Capsule Daily Dose 10 to 14 hours before retiring

Rx Only. Caution: Federal law prohibits dispensing without prescription.

Biphetamine—made and marketed ONLY by STRASENBURGH LABORATORIES ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release



• PEDIATRIC RESPIRATION UNIT

DESCRIPTION: For use with infants and small children, this device utilizes the Bennett Flow-Sensitive Valve. Features include minimal dead-air space, flexible small-bore main tube, miniature manifold and flex tube designed to be used in any position, reduced maximal flow, and interrupted nebulization. Two Bennett masks (sizes 3 and 4) for infants and a modified Bennett Type A small mask are supplied with each of the respiration units.
PRODUCER: Bennett Respiration Products, Inc., Los Angeles.

• GRISEOFULVIN

PURPOSE: Fungicide for oral administration.
INDICATIONS FOR USE: Mycotic infections of the skin, hair and nails.
CAUTION: Minor gastrointestinal symptoms, headaches, lethargy and dryness of the mouth occasionally occur. Because there have been a few cases of transient leukopenia, it is recommended that blood counts be done at regular intervals. Urticaria or other skin eruptions are rare; if they do occur the drug must be withdrawn. Infections due to yeastlike fungi are refractory to griseofulvin, and candidiasis may become worse after use of this agent.
DOSAGE AND ADMINISTRATION: Usual adult dosage is 4 tablets daily, either 1 tablet four times a day or 2 tablets twice a day. For children, 1 to 4 tablets daily, depending on age and weight. Less severe infections may require only 2 or 3 tablets daily; patients with widespread lesions may require 6 to 8 tablets initially.
HOW SUPPLIED: 250 mg. tablets in bottles of 30 and 100.
PRODUCER: Ayerst Laboratories, New York.

• VITAMIN A & D OINTMENT WITH PREDNISOLONE (New Formula)

PURPOSE: To treat inflammatory skin conditions.
COMPOSITION: Vitamins A and D and 0.5 per cent prednisolone in a lanolin-petrolatum base.
DOSAGE AND ADMINISTRATION: Topically three or four times daily. A gauze dressing may be applied over the ointment when indicated.
HOW SUPPLIED: 10 and 25 gm. tubes.
PRODUCER: White Laboratories, Inc., Kenilworth, N. J.

• PANTHO-FOAM

PURPOSE: To relieve pain, itching and inflammation in skin conditions.
COMPOSITION: 0.2 per cent hydrocortisone and 2 per cent pantothenylol as an aerosol foam.
DOSAGE AND ADMINISTRATION: Apply directly to skin two or three times a day or as needed.
HOW SUPPLIED: 2 oz. aerosol container.
PRODUCER: U. S. Vitamin & Pharmaceutical Corp., New York.

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PURPOSE: Appetite depressant and tranquilizer.
COMPOSITION: Each tablet contains 5 mg. dextroamphetamine sulfate and 400 mg. meprobamate.
DOSAGE AND ADMINISTRATION: 1 to 2 tablets one-half to one hour before meals.
PRODUCER: Wallace Laboratories, New Brunswick, N. J.

• ENGLAND FIELD FINDER

DESCRIPTION: The entire surface of this 3 by 1 in. glass slide is marked with a square grid at 1 mm. intervals. It is used on a microscope with a mechanical stage and provides an easy method of recording the position of a specimen so that it can be relocated by using the Field Finder on any microscope. Each square contains a center ring bearing a reference number and letter. The remainder of each square is subdivided into four segments numbered 1 through 4; thus, a simple notation will exactly locate a field of interest. Arrowheads on three edges of the slide serve as locating points.
PRODUCER: Edmund Scientific Co., Barrington, N. J.

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JANUARY 1960

Have You Considered Investment In The Magic 5s? That's how dealers in U. S. Government bonds refer to a new Treasury issue. The "five" comes from the interest return - 5%; the "magic" was added to reflect the tremendous appeal the issue had to the investing public. Many individuals who had never invested in a Treasury bond, other than U. S. Savings bonds, invested in this issue. Most saw an opportunity to secure a higher interest return by investing bank savings in this Government security. Still others, dissatisfied with current yields of 3% from stocks, sold part of their stock holdings to reinvest in the 5% Treasury issue.

Notwithstanding continued threat of inflation and the effect on dollar obligations such as bonds, widespread investment appeal evidenced a trend. A study of 25 major balanced mutual funds reveals that only three of the 25 added to the proportion of their funds invested in common stocks during a recent period. The others invested a greater portion in Government and corporate bonds "where rates of return are higher than they have been in over 25 years."

On Investing In A Bond - consider anticipated return, both before and after taxes. A bond paying comparatively low interest still may produce a higher return after taxes than another bond carrying high interest. Consider this example which involves a comparison of the new Treasury issue bearing interest at 5% rate with 2 1/4 Treasury bonds, maturing in June of 1962.

At the time the 5% Treasury was issued, the 2 1/4 bonds were selling at a discount. On purchase of the latter, you were assured of a 2 1/4% interest return and an additional annual return due to purchase at a discount from par of 2.5% - or a total yield over the bond's maturity of 4.75%. The 5% issue gave a greater return than the 2 1/4s before considering taxes. However, return on the 5s is fully taxable interest. If held until maturity, the return on the 2 1/4s reflects a tax-favored capital gain factor of 2.5% due to the discount - plus 2 1/4% interest. Due to the

more favored tax treatment, a doctor with taxable income of $35,000 a year would get a net return of about 3% after taxes from the 2 1/4s but only 2.5% after taxes from the 5s. If the doctor had taxable income of $20,000, the 2 1/4s still would give a greater return - a net return of 3.4% after taxes against 3.1% from the 5s. Only when the doctor's income fell below $10,000 a year would the 5s give a greater return both before and after taxes than the 2 1/4s.

When You Buy A Bond Selling For Less Than Par - you buy what is known as a discount bond. Thus, a bond which will be redeemed at 100 on maturity is said to be selling at a 15-point discount if it now can be purchased at 85. If you hold such bond until maturity and it is redeemed at par, your profit reflecting the discount is capital gain.

Many investors distrust sound bonds selling at a discount because they do not understand the reason for the discount. Assume that in financing expansion a number of years ago, a corporation was able to issue bonds carrying a low interest rate of 3 1/2% because of low prevailing rates at the time. If it or another comparable corporation issued a similar bond today, the bond would have to carry an interest return of more than 5% because prevailing interest rates have risen. Since an investor can purchase a newly issued bond giving an interest return of more than 5%, he would not be interested in purchasing a bond originally issued a number of years back and carrying an interest return of 3 1/2% - unless he could purchase such earlier issue at a discount. As a result, outstanding bonds issued a number of years ago and carrying a low interest currently sell at a discount, but such discount doesn't mean that investment involves a speculation. Such bonds may be very safe investments.

At the present time, there are a number of Government bonds which are selling at a discount (e.g., Treasury 2 1/4s, June '62). There are also many high-grade corporate bonds in the same category (e.g., A. T. & T. 3 3/8s, 1973). If you wish to invest part of your savings in dollar obligations (e.g., bonds) rather than equities (e.g., stocks), discount bonds have tax appeal. If the bonds have a comparatively short maturity date, say three or four years, you will get a return on investment which is taxed as capital gain by holding the bond until maturity.

Investment In Tax-Exempt Bonds - promises a greater return than has been available in years. It is possible to get an interest return of 3.5% or more from the highest-grade municipal bond. For a professional man with income of $10,000 a year, such return is the equivalent of a taxable return of 5%; for the individual with income of $20,000 a year, 6%. When investing in tax-exempt bonds, there are some tax points to keep in mind.

Interest on a municipal or other tax-exempt bond is not necessarily exempt from all income taxes. A New York resident who buys a bond issued by a municipality located in Pennsylvania will not have to pay any tax on such interest for Federal tax purposes. However, he will have to pay a New York income tax on the interest. If he wants to avoid New York as well as Federal tax on interest from a municipal bond, he should buy one issued by a political subdivision of New York State.

Some tax-exempt bonds are selling at a discount. A discount on a fully taxable bond such as a United States Government security or corporate bond is a favorable tax factor. Any profit reflecting the discount which is subsequently realized is a capital gain return. But a discount on a tax-exempt bond is a disadvantage. If you buy a tax-exempt bond selling at par, all of the return on investment reflects interest payments - and those interest payments are tax-exempt. However, when you buy a tax-exempt selling at a discount, part of the investment return you will realize will reflect the discount. While return on that discount is tax-favored capital gain, it is still subject to tax. By buying tax-exempt bonds selling at par, you avoid capital gains tax, secure a return which is completely exempt from Federal tax.

* * * * *

Do You Live In A State Which Has A Sales Tax? You're allowed to deduct such taxes on your Federal income tax return if you itemize deductions for charitable contributions, interest payments, etc. Most self-employed professional people will itemize deductions in filing their tax returns rather than electing the so-called optional standard deduction. If you do itemize deductions, how do you compute the amount you've paid in sales taxes on many purchases over a year? The Internal Revenue Service recognizes that this is a practical problem faced by many taxpayers. It has now taken affirmative steps to help.

The Service has authorized its various District Offices to release guidelines to be used by taxpayers in computing an average amount for state sales tax. The guideline will enable you to determine whether "estimated amount you deduct on your Federal income tax return for state sales taxes is reasonable and acceptable." The result will be to eliminate dispute between taxpayer and a reviewing revenue agent over sales tax deduction.

Some of the District Offices have been using guidelines for internal checking purposes for a number of years. The amount allowed a particular taxpayer will vary with his income and family status. Normally, a married man with children would make more purchases during the course of a year subject to sales tax than a

single man with the same income. The Service takes that into account. Thus, one District Office in a state with a 2% sales tax has held these amounts are reasonable and acceptable for a taxpayer with $6,000 income - $61 if single, $64 if married, $83 if married with one child, and $92 if married with two children. Under this guideline, the last named individual is allowed a 50% greater deduction than the single person.*

* * * * *

You Can Give Securities To A Child - using a custodian account regardless of where you live in the United States. All of the 50 states now permit such gifts to minors. It is no longer necessary to create a trust for a child on a gift of securities. Such gift is permitted either under the so-called Model or Uniform Acts enacted by all states. While the two Acts resemble each other, they are not identical. Are the differences major enough to produce different tax results? That question had been asked. In putting any doubts to rest, the Internal Revenue Service now answers favorably in a detailed ruling giving its position on income, gift, and estate tax consequences on such gifts to a child.

In all the states, income from a custodian account will be taxed to the child unless such income is used to discharge a legal obligation to support the child. Generally, that means that there would be no income tax to pay unless the custodian account produced more than $675 income in a year - $725 if all income from the custodian account came from dividends.

Regardless of whether the gift is made under the Model or Uniform Act, an annual gift tax exclusion is allowed on such gift. That means that tax-free gifts of $3,000 a year could be made to a child - $6,000 a year if the donor's spouse consents to the gift.

A donor establishing a custodian account for a child can name himself custodian. He can do that even though he is the parent of the child. However, the Service again warns that for estate reasons, the parent should name someone other than himself as custodian. Securities in the custodian account will not be taxed in the donor's taxable estate except in two situations. Gift property will not be taxed in the donor's estate unless the gift was made in contemplation of death and the donor died within three years after the gift - or unless he named himself custodian and he died before the child attained 21.

In its latest ruling, the Service did not discuss the right of a parent-donor to dependency credits where he establishes a custodian account for his child. But in the past, it made this favorable tax concession. If the parent meets the support test, he does not lose the dependency credit even though a return must be filed and tax paid for the child.

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► NEW NUTRITION BOOKS

Nutritional Diagnosis. By Grace A. Goldsmith, M.D., Professor of Medicine and Director, Nutrition-Metabolism Unit, Department of Medicine, Tulane University School of Medicine, New Orleans. American Lecture Series. 164 pages. 1959, Charles C Thomas, Springfield, Illinois. $5.50.

The Heinz Handbook of Nutrition. Edited by Benjamin T. Burton, Ph.D., Staff Consultant in Nutrition to the H. J. Heinz Company, Pittsburgh. 439 pages. 1959, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto and London. $5.75.

Principles of Nutrition. By Eva D. Wilson, Ph.D., Professor of Foods and Nutrition, Katherine H. Fisher, Ph.D., Associate Professor of Foods and Nutrition, and Mary E. Fuqua, Ph.D., Associate Professor of Foods and Nutrition, College of Home Economics, Pennsylvania State University, University Park. 483 pages, illustrated. 1959, John Wiley & Sons, Inc., New York. $5.75.

Human Nutrition and Dietetics. By Sir Stanley Davidson, M.D., Professor of Medicine and Clinical Medicine, A. P. Meiklejohn, D.M., Lecturer in Nutrition, and R. Passmore, D.M., Reader in Physiology, University of Edinburgh Faculty of Medicine, Edinburgh, Scotland. 844 pages with 24 plates. 1959, The Williams & Wilkins Company, Baltimore. $15.00.

A number of textbooks on nutrition of possible interest to the practitioner have appeared in recent months. A small handbook, "Nutritional Diagnosis," by Grace Goldsmith attempts to help physicians in the problem of detection and appraisal of nutritional problems. A first part deals with general observations, medical history, dietary history, physical examination and growth of infants and children. The discussion of physical examination is particularly worthwhile in that it gives a detailed list of those points to look for in order to detect possible nutritional deficiencies and covers these concisely and well. The list of laboratory procedures useful in nutritional diagnoses is also helpful. The sections on evaluation of dietary history and growth data are skimpy, but these limitations were probably unavoidable considering the very legitimate desire of the author to keep this volume small. While Dr. Goldsmith rightly points out that failure to meet the recommended dietary allowances of the Food and Nutrition Board (which include an appreciable safety margin for most individuals) cannot be equated with nutritional deficiencies, it would have been useful to discuss at what point low intakes of given nutrients are almost certainly undesirable. Some discussion of the fact that the margin of safety may be different for various nutrients so that it may be more dangerous to live on 50 per cent of the recommended dietary allowances for thiamine than to live on 50 per cent of the recommended dietary allowances for ascorbic acid might have been useful.

Similarly, a more detailed discussion of the value of various grids, the recent evolution of the average heights and weights of U. S. children in relation to grids which by and large were established some time ago, and some discussion of the possible nutritional significance of temporary growth failure would have been useful.

Dr. Goldsmith's chapter on caloric nutrition is extraordinarily short, even considering the limitations of the volume. Certainly caloric overnutrition as a national nutritional problem in America today deserves more than a half a page.

(Continued on page A-172)

It would have been particularly useful, for that matter, to have a discussion of obesity in childhood. The chapter on protein nutrition is well conceived and organized. The problem of the possible role of specific amino acids in nutrition might perhaps have been discussed a little more fully, but this comment probably only reflects the reviewer's particular interest. The chapters on carbohydrate and lipid nutrition are adequate and that on mineral nutrition presents a very good summary of practical knowledge. As could be expected of Dr. Goldsmith, the proportionately longer chapter on vitamin nutrition is excellent. The descriptions, signs and symptoms of nutritional deficiencies are concise yet comprehensive. In summary, this is a useful little book which will serve as a good refresher for the general practitioner interested in nutrition.

"The Heinz Handbook of Nutrition" was prepared by the executive editor, Dr. Benjamin Burton, with the help of a distinguished editorial board. The book is well planned and contains particularly thorough discussions on the utilization of food, foodstuffs, and nutrition in health and disease.

The opening section on the physiologic and psychologic aspects of hunger and absorption and digestion is particularly good. The description and discussion of the role of nutrients is thorough and highly informative. While the clinical description of nutritional deficiencies would have been enormously helped by well-chosen illustrations, it still represents a thorough and well-balanced presentation. Unfortunately, the whole book is marred by the total lack of any references to original work or to reviews. As a result of this bibliographic failure, it is this reviewer's judgment (and that of many of his colleagues) that the handbook is completely useless as a teaching text at the university or postgraduate level. The practicing physician as well as the student wants to be able to check sources and ascribe statements on new findings to some authority. One can earnestly hope that the editor and the publisher will recognize this fact, take steps to correct it, and bring forth soon a second edition which conforms to the accepted standards of scholarly presentation.

"Principles of Nutrition," by Eva D. Wilson, Katherine H. Fisher and Mary E. Fuqua, does very well the extraordinarily difficult job of teaching nutrition to beginning students. It is designed for the intelligent person with little technical background and manages to convey information in a simple form while indicating the amount of research that has gone behind each statement. It gives enough references to permit the student to check for himself some of the facts presented. The book is attractively presented and clearly printed with excellent illustrations, both schematic and photographic. It has particularly good discussions of the social aspects of nutrition, nutrition in aging, nutrition in growth, food budgets, etc. A book of this sort is the best answer the medical profession has when dealing with food faddists. Patients with an interest in nutrition ought to be encouraged to read it so that they can find out for themselves not only a summary of the present knowledge of nutrition, but also how this knowledge was arrived at.

The large textbook by Davidson, Meiklejohn and Passmore, "Human Nutrition and Dietetics," is the best text on nutrition available to the advanced student or to the internist with an abiding interest in the subject. It is divided into six main sections: Physiology, Food, Primary nutritional diseases, Nutritional aspects and dietetic treatment of general diseases, Public health, and Diet and physiologic stress. The first part deals with the more classic aspects of the biochemistry and physiology of nutrition, including the mechanism of regulation of food intake. The references as well as the illustrations are judiciously chosen, and the book meets the highest requirements for scholarship in every respect. That it does so without being unusually wordy is particularly well illustrated by chapter 7 (Alcohol) which in the space of only two and one-half pages manages to give a superb summary of present knowledge of the position of alcohol in nutrition.

The only major reservation this reviewer has on the long (265 page) first section is that once again a better discussion of the significance of recommended dietary allowances of nutrients could have been provided. A second part on foods is particularly useful. It gives a good description of the various types of food into which, ultimately, nutrition is translated. There is a useful section on preserving, cooking and wastage, as well as a section on food poisons. The discussion of subnutrition and starvation could have been amplified, perhaps, as could have the section on obesity, particularly in view of the author's great personal competence in caloric nu-

(Continued on page A-174)

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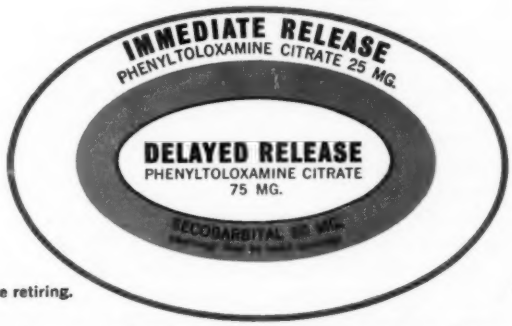

DOSAGE: 1-2 tablets before retiring.

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REFERENCES: Batterman, R. C., et al.: New York J. Med. 58:3821, 1958. / Harrison, T. R.: Principles of Internal Medicine, ed. 3, New York, McGraw-Hill, 1958, p. 1764. / DiMascio, A., et al.: Am. J. Psychiat. 115:301, 1958. / Sainz, A.: Proc. Mohawk Valley Psychiatric Assn., June 17, 1957. / Fleischmajer, R., et al.: Antib. Med. & Clin. Therap. 5:120, 1958. / Hoekstra, J. B., et al.: J. Am. Pharm. A. 42:587, 1953. / Cronk, G. H., and Naumann, D. E.: New York J. Med. 55:1465, 1955. / Paper in preparation: Data on 500 clinical cases. (Available on request.)

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trition. The sections on nutritional deficiencies are good and particularly well illustrated. Section 4, Nutritional aspects and dietetic treatment of general diseases, is excellent, though it may perhaps reflect too much Britain's practices for literal application to American institutions.

Part 5, on public health nutrition, is excellent. It wisely appraises the social as well as the technical factors to be taken into account when dealing with nutritional practices of populations.

A final, and very brief, section deals with diet and physical stress. The description of the management of children's diets could have been somewhat more detailed and again some criteria of evaluation of adequacy of diet for growth could have been discussed at somewhat greater length. Other chapters in this section, dealing with athletics, effects of climate, expeditions and emergency rations, are consistent with the excellent quality of the book. Again, this volume cannot be recommended too highly for the internist with special interest in nutrition.

J. M.

► BIOPSY MANUAL

By James D. Hardy, M.D., Professor and Chairman, James C. Griffin, Jr., M.D., Assistant Instructor, and Jorge A. Rodriguez, M.D., Assistant Professor of Surgical Anatomy, Department of Surgery, University of Mississippi School of Medicine, Jackson. 150 pages with 54 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $6.50.

The purpose of this manual is to describe the indications for and technics used in performing a biopsy, as well as precautions to be taken and potential errors and complications that may occur. The experience of the authors and of many surgeons shows that biopsies may be inadequate, mislabeled, incorrectly preserved or lost. The importance of an adequate biopsy is stressed, since in performing frozen section examinations the pathologist can report only on the material submitted for study. If a correct diagnosis cannot be established by the frozen section technic, it is recommended that this be followed by paraffin studies. The importance of the working team of pathologist and surgeon is emphasized.

The subject matter, which includes discussions of biopsies in the entire body except for the central nervous system, is covered in 12 chapters. The manual is easy to read, is illustrated with line drawings, and contains an index and a bibliography.

S. A. L.

► DIAGNOSTIC RADIOISOTOPES

By Charles A. Owen, Jr., M.D., Section of Clinical Pathology, Mayo Clinic, Rochester, Minnesota. 425 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $15.75.

Concerned solely with diagnostic tests using radioactive elements and compounds, this text does not consider therapeutic applications. Discussion of the basic principles of radiophysics and radiochemistry is kept to a minimum. The physiologic principles of the various well-established diagnostic procedures are emphasized, and the technics employed in these tests are discussed in detail. Newer, less well-established tests are outlined less completely.

The volume includes chapters on measuring radioactivity, metabolism, hematology, localization of tumors, the gastrointestinal tract, the cardiovascular system, general applications of radioisotopes, the hazards of radiation, and federal regulations. The text is well documented; the section on the thyroid alone lists 528 references. Several useful tables and charts are included in the appendix.

J. W. J. C.

► THE YEAR BOOK OF MEDICINE (1959-1960)

Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D. and Philip K. Bondy, M.D. 733 pages with 110 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

As in the past, this book consists of abstracts of recent articles which cover a wide variety of subjects. Sections are devoted to infections; the chest; blood and blood-forming organs; the heart, blood vessels, and kidneys; the digestive system; and metabolism.

The text is well illustrated, and there are numerous editorial comments.

R. V. R.

(Continued on page A-176)

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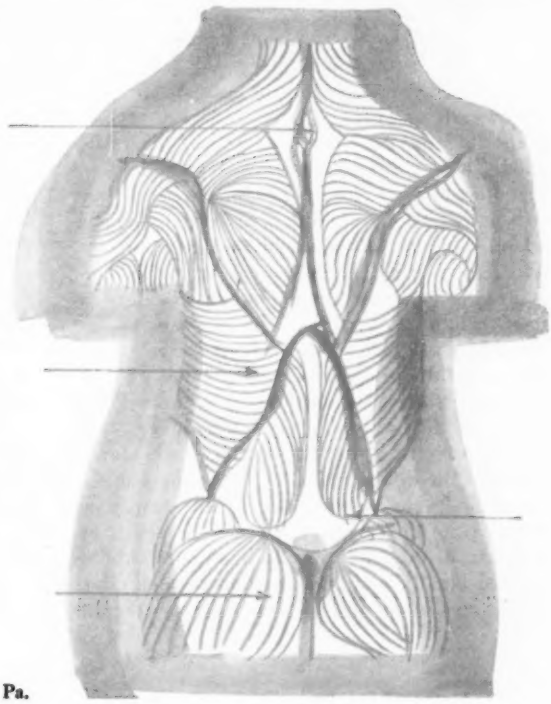

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► GRAY'S ANATOMY OF THE HUMAN BODY

Edited by Charles Mayo Goss, M.D., Professor and Head of the Department of Anatomy, Louisiana State University School of Medicine, New Orleans. Ed. 27. 1,458 pages with 1,174 illustrations, mostly in color. 1959, Lea & Febiger, Philadelphia. $17.50.

It is difficult to appraise accurately any edition of this text for two reasons: (1) The bulk of the volume makes it impossible for a reviewer to read it thoroughly, and (2) many reviewers, like myself, not only have used "Gray's" for years as one of the standard texts but were brought up on it and in those early, unsophisticated years regarded it as a veritable bible. I am further handicapped in evaluating this book by my belief that a textbook intended primarily for medical students should approach the subject in somewhat the manner in which it is usually taught. Thus, a systemic anatomy, unless it is frankly a reference book, is somewhat anachronistic, however refreshing it may have been in Gray's time.

This is the third edition edited by Professor Goss, a capable and distinguished anatomist, and he has, as before, improved the text. The revisions in the present edition consist primarily of a thorough rewriting of the section on the central nervous system, considerable revision and rearrangement of the discussion of the vascular system, and a few minor shifts in the position of material in other sections. The lists of references at the ends of chapters have also been revised. Some illustrations have been added, others deleted. There will probably be general agreement that most of these changes are for the better.

It is disappointing that four years after the adoption of the new international anatomic terminology (Paris, 1955), a work as widely used and highly regarded as this one does so little toward helping to establish this terminology. To the older reader who uses the book for reference, this is of little moment; however, those who are teaching freshman medical students and who are trying to adjust to the new terminology will probably find this text frustrating. I am acutely aware of the difficulty inherent in using the new terminology consistently, and I can sympathize with slips of the tongue and pen when one is attempting to do so. However, if authors, editors and teachers do not make a wholehearted effort to use and teach this new terminology, the International Anatomical Nomenclature Committee will have succeeded only in giving us another set of synonyms to add to the BNA, the British Revision, the Jena Revision, and so forth.

The failure to make better use of the new terminology is undoubtedly due in part to the limited time and energy of the editor and in part to the impossibility of relabeling all the illustrations; however, many lapses and inconsistencies can be cited. For instance, no attempt has been made to reclassify the joints, which would have involved only a change in the text. Very commonly the BNA term is given in boldface type, as if it were preferable, while the new and preferred term is given in parentheses, often with other synonyms, so that the student has no way of knowing what is the proper terminology.

To the older student of medicine, all this is academic. For him, the new edition of "Gray's" will prove to be a well-written, up-to-date volume that he can consult on many questions of anatomy. It is not so clearly suited for the beginning student, for whom it was designed. If I had a son entering medicine, I would probably advise him to acquire this book or its comparable rival, but I also would hope that he would have another text for regular study.

W. H. H.

► DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY

By S. Leon Israel, M.D., Professor of Gynecology and Obstetrics, University of Pennsylvania Graduate School of Medicine, Philadelphia. Ed. 4. 666 pages with 147 illustrations. 1959, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $15.00.

In assuming the authorship of this well-known textbook, Dr. Israel has almost completely revamped the text and, in addition, has added chapters on the adrenal and thyroid glands and the androgens.

Although the subject matter is comprehensive, the author has maintained the clinical approach by emphasizing those points most frequently encountered in general practice. The chapter on the male's role in infertility has been rewritten by Dr. Charles W. Charney.

E. A. B.

(Continued on page A-178)

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*Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. *61*:71-74 (Jan.) 1951.

†Projected estimate from data of U.S. Office of Vital Statistics indicated that 3 out of 4 births in 1958 were to multiparas.

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► THE ANATOMY OF THE NERVOUS SYSTEM
Its Development and Function

By Stephen Walter Ranson, M.D., late Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago. Revised by Sam Lillard Clark, M.D., Professor and Chairman of the Department of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee. Ed. 10. 622 pages with 434 illustrations, 11 in color. 1959, W. B. Saunders Company, Philadelphia and London. $9.50.

Since 1920 this volume has been a favorite textbook of human neuroanatomy, and it has been used widely in medical schools. The format of this latest edition is unchanged. The extensive changes in anatomic terminology adopted by the International Anatomical Nomenclature Committee in 1955 have had little effect on the nomenclature of neuroanatomic structures.

There are relatively few major alterations in this edition in the handling of the bulk of human neuroanatomy. The most prominent changes are in the description of reticular formation and the correlation with newer neurophysiologic concepts. This has been necessary to bridge the gap in knowledge between the anatomist's conception of reticular formation as a diffuse structural system and the physiologist's functional concepts of this scattered and poorly understood system.

The rhinencephalon is viewed more as the "old" brain; less emphasis is placed on its olfactory function and more is placed on its role in visceral and emotional mechanisms. The chapter on the thalamus has been somewhat simplified.

The chapter on the vascular supply of the central nervous system now includes a section on the vessels to the spinal cord. There are a few electron micrographs of neurons, nerves and neuroglia, as well as several new illustrations.

The diagrams of fiber tracts have again been oversimplified to suggest that these tracts are well-localized compact groups. Only late in the text is it implied that these tracts are more widespread and that they overlap into other fiber systems. The student also will have difficulty in understanding the fiber systems related to voluntary, automatic and reflex eye movements.

The excellent outline for a laboratory course and the well-known clinical illustrations are unchanged. The text is fairly well documented and includes a bibliography of major articles for further reading by the student.

R. E. Y.

► CORONARY HEART DISEASE

By John William Gofman, M.D., Professor of Medical Physics, The Donner Laboratory, University of California, Berkeley. 353 pages. 1959, Charles C Thomas, Springfield, Illinois. $8.00.

Dr. Gofman has been particularly interested in the detailed study of plasma lipoproteins as determined by ultracentrifugal methods. In his book he has emphasized the importance which he attaches to his findings regarding the lipoprotein fractions. He is not concerned with the clinical symptoms of coronary artery disease, but with the so-called subclinical phase of the disease and the need for dealing with coronary heart disease as a medical problem before it is manifested clinically.

Regarding the identification of factors in the development of coronary heart disease, the author concluded that the only factors that still stand critical testing for providing independent information about the risk of clinical coronary heart disease developing in an individual are the blood levels of the lipoprotein fractions and the diastolic blood pressure.

Many other data are supplied regarding the effect of "independent factors" which may be associated with the development of subclinical coronary heart disease.

Dr. Gofman believes that the blood cholesterol gives less definitive information regarding the prediction of development of coronary atherosclerosis than does the estimation of the various blood lipoprotein fractions as determined by ultracentrifugal studies. He wrote, "Determination of the blood cholesterol will not provide the requisite information for the effective prosecution of a program for the prevention of clinical coronary heart disease." It is probably true that this view is not widely accepted by physicians interested in the pathogenesis and treatment of coronary artery disease.

The book contains a large amount of data and references and should be valuable to the physician interested in coronary artery disease and the factors underlying its genesis.

D. C. C.

(Continued on page A-180)

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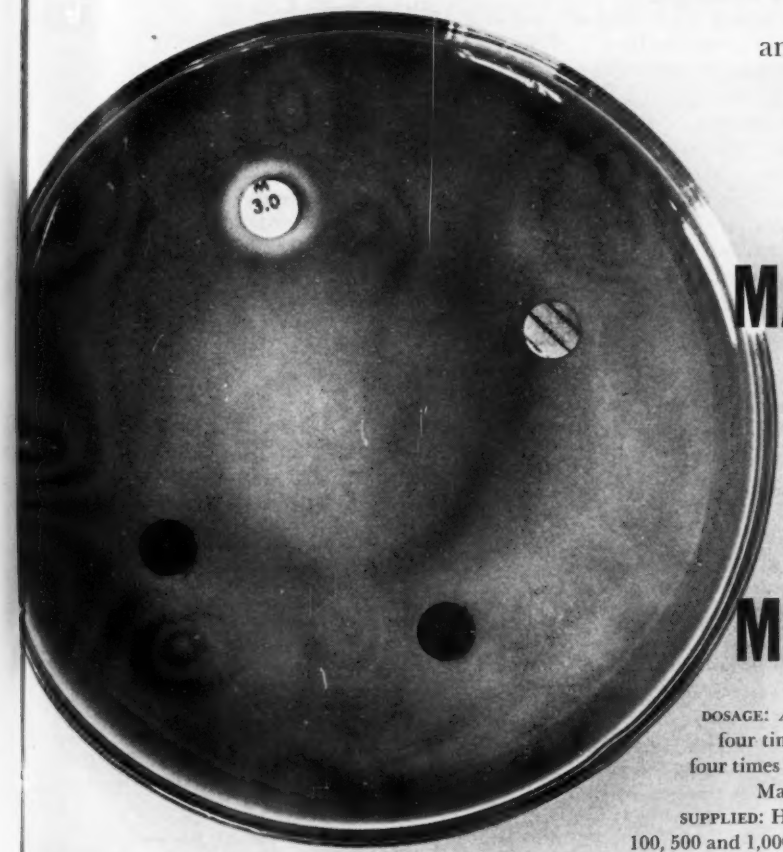

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► DIAGNOSIS OF CONGENITAL HEART DISEASE

By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe and Bengt Jonsson, Pediatric Clinic, Karolinska Sjukhuset, Stockholm, Sweden. Ed. 2. 866 pages with 727 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $28.00.

The case material discussed in the second edition of this detailed work is almost double that of the first; it includes clinical and roentgenologic studies of 742 cases of congenital heart disease. The authors have made "further differentiations in certain types of heart disease," largely through their own methods of examination. They state that they have tried to extract the most valuable and topical data from the extensive literature which documents the advances in cardiology, and they list 727 separate references. It is important to note the limitation in the authors' intent; they intend this book to be an account of their own observations, not a comprehensive survey of the literature.

The volume begins with a survey of the circulatory system of the embryo, which is meant to provide an embryologic background to make the congenital malformations more understandable. Despite disclaimers, the survey is, in fact, quite detailed and is documented with some excellent roentgenographic correlations. Following this is a technical introduction to the roentgenologic anatomy and physiology of the heart and the methods employed for diagnosis at the Karolinska Institute.

The case material is arranged for systematic presentation of specific disease entities, beginning with pulmonary stenosis. The individual sections are well illustrated with the excellent angiocardiographic material for which these authors are justly famous. The diseases are discussed with completeness and clarity.

When considering the limitations of this book, it is necessary to mention only those stated by the authors themselves. Their subject is congenital heart disease in children, and their material is primarily their own experience. Thus, the problems of congenital heart disease in adults do not receive detailed treatment. In addition, approaches to these problems common to other medical centers are given little notice. In spite of the stated limitations, it was disappointing to see that the entire subject of indicator dilution curves is ignored.

Perhaps the title of the book suggests too great a scope. It is still excellent, however, and deserves a place in the library of anyone seriously interested in congenital heart disease.

J. A. C.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are received more extensively.

A Synopsis of Anaesthesia. By J. Alfred Lee, M.R.C.S., Senior Consultant Anaesthetist to the Southend on Sea Hospital, England. Ed. 4. 616 pages with 72 illustrations. 1959, The Williams & Wilkins Company, Baltimore. $6.50.

Rheumatic Fever; Epidemiology and Prevention. Proceedings of a seminar at the International Children's Centre, Paris, 1956. Edited by R. Cruickshank, M.D. and A. A. Glynn, M.R.C.P. 193 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $5.50.

Maternal Disorders Related to Fetal Stress, Perinatal Death and Congenital Defects. Public Health Bibliography Series. Compiled by Elizabeth Koenig, Reference Librarian, National Institutes of Health, Bethesda. No. 25. 33 pages. 1959, U. S. Government Printing Office, Washington, D.C. $0.15.

Clinical Prosthetics for Physicians and Therapists. By Miles H. Anderson, Ed.D., Director, Prosthetics Education Project, Charles O. Bechtol, M.D., Professor of Surgery (Orthopedics), and Raymond E. Sollars, Associate Director, Prosthetics Education Project, University of California at Los Angeles School of Medicine. 393 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $10.50.

Trifluoperazine; Further Clinical and Laboratory Studies. Twenty-one reports with an introduction by John H. Moyer, M.D., Professor of Medicine and Chairman, Department of Internal Medicine, Hahnemann Medical College and Hospital of Philadelphia. 191 pages. 1959, Lea & Febiger, Philadelphia. $3.50.

Medical Radiographic Technic. Prepared by the Technical Service of the X-ray Department, General Electric Company, Milwaukee, under the editorial supervision of the late Glenn W. Files. Ed. 2. 386 pages with 366 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $11.00.

A Guide to Antibiotic Therapy. By Henry Welch, Ph.D. 69 pages. 1959, Medical Encyclopedia, Inc., New York. $3.00.

Synopsis of Ear, Nose and Throat Diseases. By Robert E. Ryan, M.D., Department of Otolaryngology, St. Louis University School of Medicine, St. Louis, William C. Thornell, M.D., Assistant Professor, Department of Otolaryngology, University of Cincinnati College of Medicine, Cincinnati, and Hans von Leden, M.D., Assistant Professor of Otolaryngology, Northwestern University Medical School, Chicago. 383 pages with 59 illustrations. 1959, The C. V. Mosby Company, St. Louis. $6.75.

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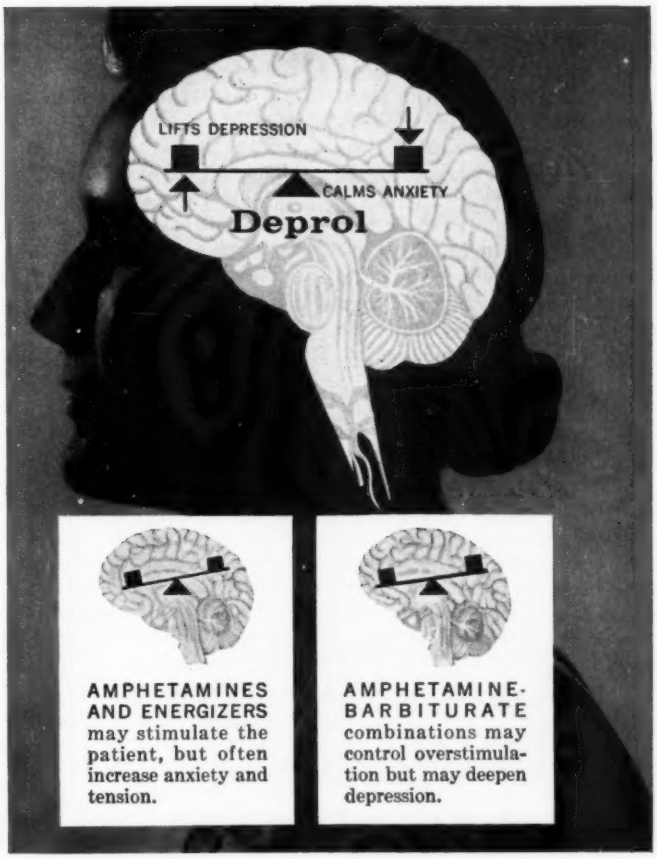
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AMPHETAMINES AND ENERGIZERS may stimulate the patient, but often increase anxiety and tension.
AMPHETAMINE-BARBITURATE combinations may control overstimulation but may deepen depression.

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DOSAGE: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Nov. 1—From Washington to Detroit by Capital Airlines and came to the Willow Run airport, which is 34 miles from the city. So to the home of B. Goldberg for a Sunday brunch with many guests and all the fish delicacies were provided by Kozloff, who owns the Booth Fisheries. In the afternoon interviews with the press and at night to speak to a great audience in behalf of the Institute for Advanced Medical Learning of the City of Hope. Great sums were contributed along with a Buick ambulance.

Nov. 2—By American jet to Chicago, leaving from Detroit Metropolitan Airport, which is just half as far from the city as is Willow Run. At noon to meet with the board of Lyric Opera and in the evening with Georgianna Richards and Sylvia Covet to the Tower Club to dine and then to hear a Czechoslovakian opera in English called "Jenufa."

Nov. 3—In the afternoon to the Palmer House, where the Interstate Postgraduate Medical Association held its meeting, finding it well attended and with great interest of all who were present. Met here Dr. Ryatt of Santa Ana, California, who noted for his lady that there really was such a person as old Dr. Pepys. So conferred with all the people from the staff of POSTGRADUATE MEDICINE and welcomed by many exhibitors, noting particularly that new young men are gradually replacing the oldsters with whom old Pepys has met these many years.

Nov. 4—Early to participate in the Don McNeill Breakfast Club and found here Dr. Jennings of Long Beach, California, who spoke on behalf of the American Association of Blood Banks. In the afternoon came Miss B. J. Ross to interview old Pepys for the V.I.P. program. At night with Dr. Louis Mann and his lady Ruth to dine at the Tower Club and then to witness a performance of the "Masked Ball," so perfect that it was a veritable triumph with ovation after ovation for Tito Gobbi, Di Stefano, and Birgit Nilsson.

Nov. 5—To a luncheon with Dr. and Mrs. George LeRoy of the Child and Family Services organization and here heard Judge George Edwards of the Supreme Court of Michigan discuss "The role of the juvenile court in contemporary society." His devotion was revealed in his choice of cases reported and in his presentation. In the evening to hear the Chicago Symphony Orchestra.

Nov. 6—To the Standard Club for a luncheon in promotion of the annual meeting of Brandeis University. In the evening to dine with Judge Isidore Brown and his most hospitable lady. Here were Judge Touhy and others, including a special guest, Douglas Crafts Watson, who spoke of his travels and of the difficulty of conducting a tour, Mrs. Harold Strauss, an interested listener, and also Peterson and Loucks. John Sheinin displayed proudly to old Pepys the perfect record of the graduates of the Chicago Medical College in examinations around the nation.

Nov. 7—All this day at the desk reading new works, in particular relating to the "Virus Hunters" and to what was called "Diseases of Medical Progress," better known as iatrogenic diseases. Watching also football on television, and for those of advanced years it is much better than sitting out in the stands in the cold and the rain.

Nov. 8—By the early plane to Minneapolis and then with Sylvia Covet to lunch at Teresa Cohen's, she preparing particularly a new dish known as *quiche Lorraine*, and it was tasty indeed. In the afternoon at my reading and in the evening to a cocktail party and dinner at the Standard Club. Here the directors and staff of Mount Sinai Hospital entertained the senior class of the University of Minnesota Medical School.

A cake was presented to Moses Barron for his seventy-sixth birthday, and he is as alert and fresh as ever. So old Pepys spoke to the class on "The evolution of quackery." Steve Barron, the pathologist, told of the work of the hospital as did Mandelstam, the superintendent, and then the latter drove old Pepys to the airport.

Nov. 10—By the early morning jet to New York. In the afternoon meeting with Paul Warwick, just returned from Europe, and also Dr. Beckley, Fredrus Baldwin and many others of his staff. Next came Dr. Algernon Reese to speak of his great work on tumors of the eye. In the evening to dine as usual with all the pleasures of the palate at Daniel's. Then to see Dore Schary's

(Continued on page A-200)

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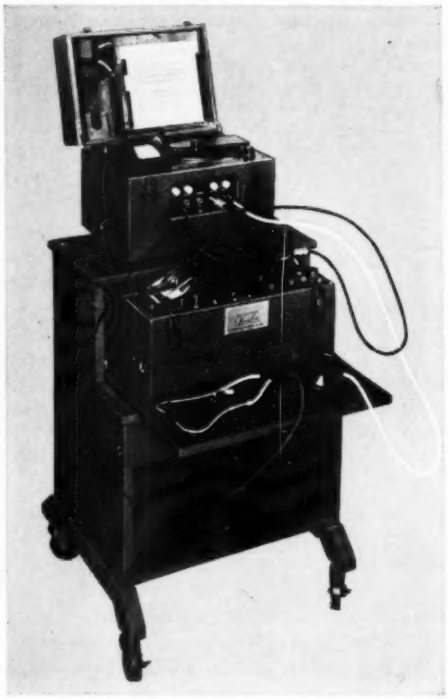

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With this portable instrument the Doctor hears the amplified heart sounds through binaural ear phones, while he views their pattern on a long persistence cathode tube screen. What he sees and hears may be permanently recorded on a paper-thin magnetic disc. Such records may be filed with the patient's history, mailed to a consultant or played back for future study.

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new play "The Highest Tree," which deals with a patient who has leukemia and has been given but six months to live. The part of the patient was played well by Kenneth McKenna, and the play is a magnificent preachment against the kind of experimentation with radioactivity that may well-nigh destroy mankind.

Nov. 11—Quite early with Bill Lasdon off to Morris Plains, discussing many problems en route. There meeting with Elmer Bobst, Al Driscoll, Bill Marsden, Whitney, Ellwood Douglass and many more and concerned with problems of publishing and research. In the evening to dine at "21" and then to a preview of one of the greatest productions of this season, the new Hammerstein-Rodgers play "The Sound of Music."

In between the acts met Russell Crouse, with whom old Pepys played poker at least a score of years ago, and congratulated him on the brilliance of the book and the marvels of the production.

Thereafter again to "21" until 2 A.M. with Bill, Milton and Stanley Lasdon and their lovely ladies and Milt Freiwald come from Philadelphia with Nan.

Nov. 12—To breakfast came Bill White and Max Geffen and all the morning spent on our project for 1960. At noon to lunch came Mark Soroko, and then in the afternoon another conference with the Warwick & Legler confreres. In the evening to dine at Sardi's with B. A. and Alice Goodman and then to see "The Miracle Worker," the early life of Helen Keller, played by a child genius named Patty Duke, and her teacher, Ann Sullivan, played by Anne Bancroft. Between the acts met Dore Schary and his dear lady and talked to them of the play and what it meant, and he was bursting with admiration for the qualities of this splendid performance.

Nov. 13—Quite early to the bookstores and then to meet with Paul Hoeber at Harper's and also Eunice Stevens and talked to them about new books. After that to sit with Herbert Mayes, finding him enthralled as always with his work, and at noon to the airport for the ride back to Chicago. In the evening to dine sumptuously with the Judge Braudes and here were some 40 guests, this being the Judge's twenty-fifth year on the bench. Toasts were offered by Dean Levy of the University of Chicago and Judge Ulysses Schwartz and many others.

With Irv Kupcinet and Harris Perlstein talked, while a ring of auditors listened, about the cranberry fiasco, if that is what it is, and surely the time has come to call a halt on sensational announcements of the hazards of our modern living.

Nov. 14—At the desk and in the afternoon watching a terrific football game in which Illinois in the last six seconds defeated Wisconsin. In the evening to the Civic Theater to see "Mary Stuart," played with Eva Le Gallienne and Signe Hasso, who performed gloriously.

Nov. 15—To do a V.I.P. program on television for Norman Ross and met there Jules DuBois of the *Chicago Tribune*, who has been much in the news concerning his reporting from Cuba; how sad it is that this beautiful little country should be so desperately torn by the striving for leadership.

Nov. 16—All this day at the desk and in the evening with Judge and Adele Braude to hear sung "The Flying Dutchman," in which Birgit Nilsson was so superior that the men of the cast seemed by contrast almost second-rate.

Nov. 17—Again all this day at the desk, and come nightfall to the Blackstone where was the annual dinner of the Brandeis University Club. Here old Pepys presided, introducing General Alfred Gruenther and thereafter the great President Sachar. Louis Mann gave the invocation and we recalled the days of 1919 and 1921, when Louis Mann was director of Hillel, and Sachar, of the University of Illinois, established its great chapter.

General Gruenther is a brilliant speaker with a heart full of compassion for all the peoples of the world. He is a master of detail with a remarkable memory

(Continued on page A-202)

AT THE BRIDGE TOURNAMENT

She was a waitress at the big bridge tournament. Suddenly she arrived with a big tray and placed three large sandwiches on the table. "What's this?" asked North. "We didn't order anything!"

"Well," she said, "when I came to get your order somebody said, 'Three clubs,' and here they are."

* * *

HISTORICALLY SPEAKING

"At the beginning of the last century Caleb Parry of Bath, who described Graves' disease before Graves did and recognized Hirschsprung's disease before Hirschsprung was born, wrote: 'It is more important to know what sort of patient has the disease than what sort of disease the patient has.'"—John Apley at Southampton.

* * *

Kindly doctor (pinching little boy's calf): And who has nice, chubby, pink legs?

Little boy: Mamma.

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and with a tremendous fund of knowledge acquired from voracious reading.

Nov. 18—By jet to San Francisco where to the airport came Dr. J. Garrott Allen and his lovely lady, and with them to San Francisco. Next to meet Leon Adams and to converse with him on public relations for some hours, after which to the dinner of the Society of Medical Friends of Wine, given in honor of old Pepys. Presiding was Dr. Robert T. A. Knudsen and among those present was my old friend Salvatore P. Lucia, who wrote the excellent book "The Medical Uses of Wine," and next sat Dr. Charles P. Mathe, with whom I journeyed to South America in 1935. Accompanying the dinner were some excellent wines and by the time old Pepys spoke, each person had participated in at least 10 or 12 glasses in all of these gorgeous vintages.

Meantime Mistress Pepys was off with Mrs. Oscar Hawkinson and Jessica Greengard to observe the growing of orchids, returning late highly decorated with her favorite blossoms. So sat late with Dr. Hawkinson, Mrs. Greengard and all the ladies.

Nov. 19—By the early morning plane to Los Angeles and then a long drive to the Huntington-Sheraton Hotel in Pasadena. In the afternoon came the officials of the City of Hope for a conference and with them Drs. Bing and Chamberlain.

Nov. 20—To walk in the gardens and to view the shopping center of Pasadena. Next to the Farmer's Market for a luncheon, and this surely one of the most amazing Americana in our land. In the afternoon came Whitaker, Cowdry, Wermer and the committee of the City of Hope, and we discussed the Institute for Advanced Medical Learning. Then to dine at Perino's.

Nov. 21—By the morning plane to Denver, where at the airport were Frank and Kraft. With them to view the Mental Health Center, which they have founded for borderline cases in young adults, this being the beginning of a venture much needed in current psychotherapy. Thereafter to the National Jewish Hospital, meeting with Phil Houtz and Dressler, and with the latter to see the new departments of occupational therapy and the new laboratories. Next to a cocktail party at the home of Dr. Kraft and here came many old friends and new ones among the medicos of Denver, including Drs. Zarit, Guggenheim, Galvin and Gaskill, who have a special interest in the Mental Health Center.

Nov. 22—To view with Mrs. Edelson the changes taking place in the JCRS, which has now become the American Medical Center; its Texas Pavilion is occupied almost wholly with terminal cases of cancer. Nearby is the breaking of ground for the Eleanor Roosevelt Research Center. Here again viewing some of the older buildings and wondering what will eventually become of all of the tremendous facilities for the care of tuberculosis. Next to luncheon at the Mental Health Center with its board of directors, and spoke to them for some time of possibilities and needs. After that by Boeing jet in two hours back to Chicago.

Nov. 23—All this day busy with reading and my scrivening. Finished "The Rack," which is the story of a tuberculosis sanatorium in southern France so horrifying in its detail of methods of treatment that one shudders to think that such sanatoriums might exist anywhere.

In the evening with Dr. and Mrs. Leon Jacobson to hear "Thais" sung by the Lyric Opera, and the playing of the "Meditation" was so sympathetic as to be in itself worthy of all the time spent.

Nov. 24—Reading now "Advertisement for Myself," by Norman Mailler, which is a self-analysis of an author as to how and why he writes and what the editors do to him. In the evening to a great *fiesta* for the benefit of the charities, which included a style show in which many of our friends modeled, and naturally sought our own Ann, who is the wife of Justin and who made a most marvelous appearance.

Nov. 25—To be interviewed

(Continued on page A-204)

GERIATRICS

Mr. Gotrocks tried desperately to get his grandfather admitted into a nursing home, but the place was overcrowded.

"Please!" he pleaded. "My grandfather is impossible to live with! All morning he sits in the bathtub, playing with a rubber DONALD DUCK®."

"Well, perhaps he's a bit senile. But he's doing no harm, is he?"

"Harm, shmarm," shouted Gotrocks. "It's *my* Donald Duck!"

* * *

There was a young lady of Kent
Who said that she knew what it meant
When men asked her to dine,
Gave her cocktails and wine.
She knew what it meant—
but she went!

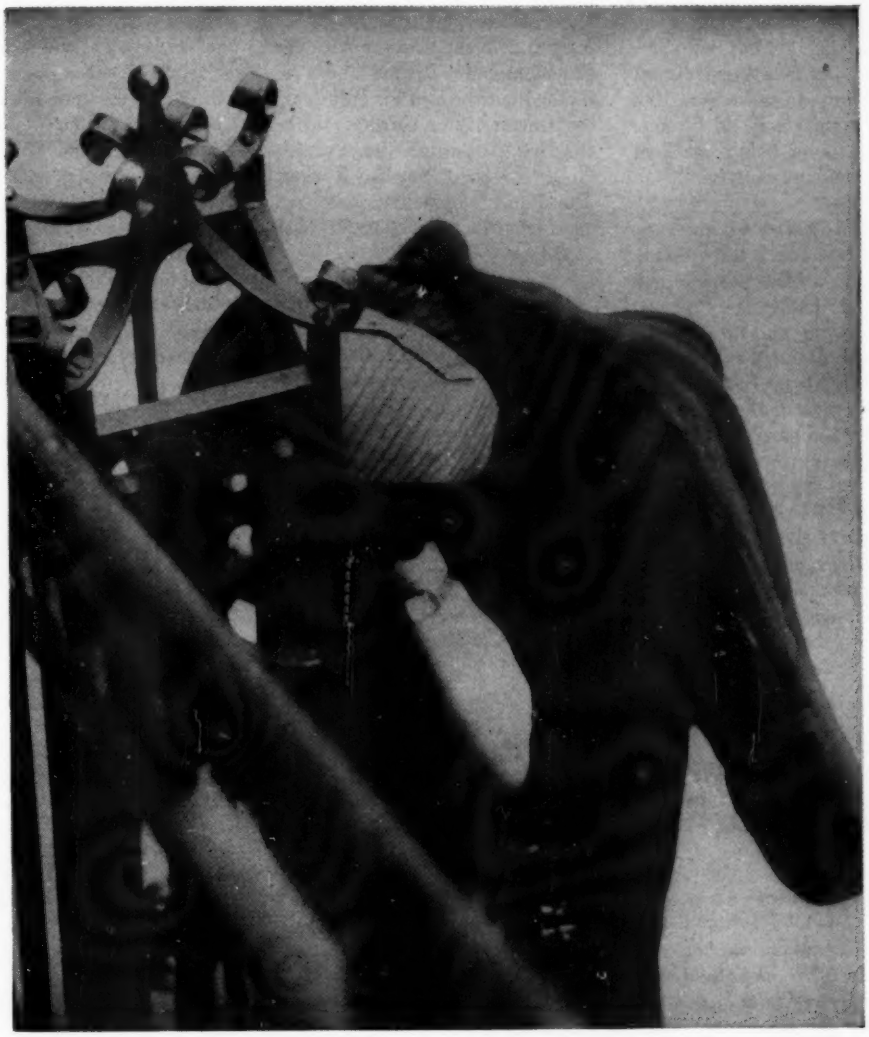
* * *

ABE MARTIN SAID

"When you consider what a chance women have to poison their husbands it's a wonder there hain't more of it done."

* * *

WHEN BLOOD PRESSURE MUST COME DOWN...



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SUPPLIED: *Tablets #2* (standard-strength), each containing 0.2 mg. of Serpasil and 50 mg. of Apresoline. *Tablets #1* (half-strength), each containing 0.1 mg. of Serpasil and 25 mg. of Apresoline. *Samples available on request.*

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by Bob Elson on station WCFL and for a half-hour we talked of medical progress and what is happening in cancer, rigging on television, and similar subjects. In the evening to a great dinner at the Blackstone, where the Franklin Kahns and Ed Singers were hosts, food being excellent and the company convivial.

Nov. 26—Thanksgiving Day, and there is so much to be thankful for, with all the projects riding high and handsome. So came all of the family and the Akcasus from Istanbul and the Hoffmans from the Hektoen Institute and Clark Kissinger from Kentucky, and the 28 made merry with good food and friendship.

Nov. 27—In the afternoon with Silvia Leiferman to greet Selman Waksman and his lady at the airport, and took them to the Ambassador after the newspapers satisfied their desire for pictures and interviews.

Nov. 28—Again at the scrivening and in the evening with the Waksmans, the Tatums and Professor Burrows and his lady from the University of Chicago to the Empire Room of the Palmer House to hear Sophie Tucker. The dinner which Fritz prepared especially for the occasion was of the very best.

Nov. 29—To brunch at the Standard Club came the Tatums and Waksmans and Professor Neff of the University of Chicago. Then all to visit the apartment and after that the University of Chicago and the Museum of Science and Industry. In the evening to cocktails and dinner at the Ambassador, where Pat Hoy entertained. Here was the Salute to Medical Research, with old Pepys as the toastmaster and Karl Meyer as the general chairman. Citations and awards were given to Selman Waksman for streptomycin, Tatum and Beadle for genetics, and Steven O. Schwartz for his work on leukemia. These were presented by Cowdry, J. Roscoe Miller of Northwestern, and Mrs. Mildred Romanoff, who presides for the Women's Auxiliary of the Hektoen Institute. A special citation to Mrs. Mary Lasker for her great leadership in the field of philanthropy and in the stimulation of increased appropriations for medical research was most felicitously presented by Governor Adlai Stevenson, whose wit and diction were especially the envy of old Pepys.

Nov. 30—All this day and in the evening catching up with the editorial stint and read a great novel from France called "Psyche 59," by Francoise des Ligneris.

The Medical Muse

RICHARD ARMOUR

VISITING HOURS

Visiting hours are the hours they post,
The time when the patient can act as host
To friends and relations who crowd up near him
And give him candy and flowers to cheer him.

Visiting hours, when these visitors close in,
Are closely guarded and carefully chosen
To keep the patient from day-long grinnin'
And let the nurses change bedpans and linen.

Yes, visiting hours are, for very good reason,
A definite period, limited season,
Which, filling the halls with their shouts and laughter,
Most visitors come just before or just after.

LINES WRITTEN ON A PLASTIC TYPEWRITER

Since plastic takes the place of wood
And sometimes even steel,
You can't tell what is plastic now
By look or even feel.

The baby has a plastic crib,
The child has plastic toys,
And in a plastic coffin one
Concludes one's earthly joys.

And so, as plastic articles
Encroach and spread and burgeon,
It frightens me to hear it said,
"Why, he's a plastic surgeon."